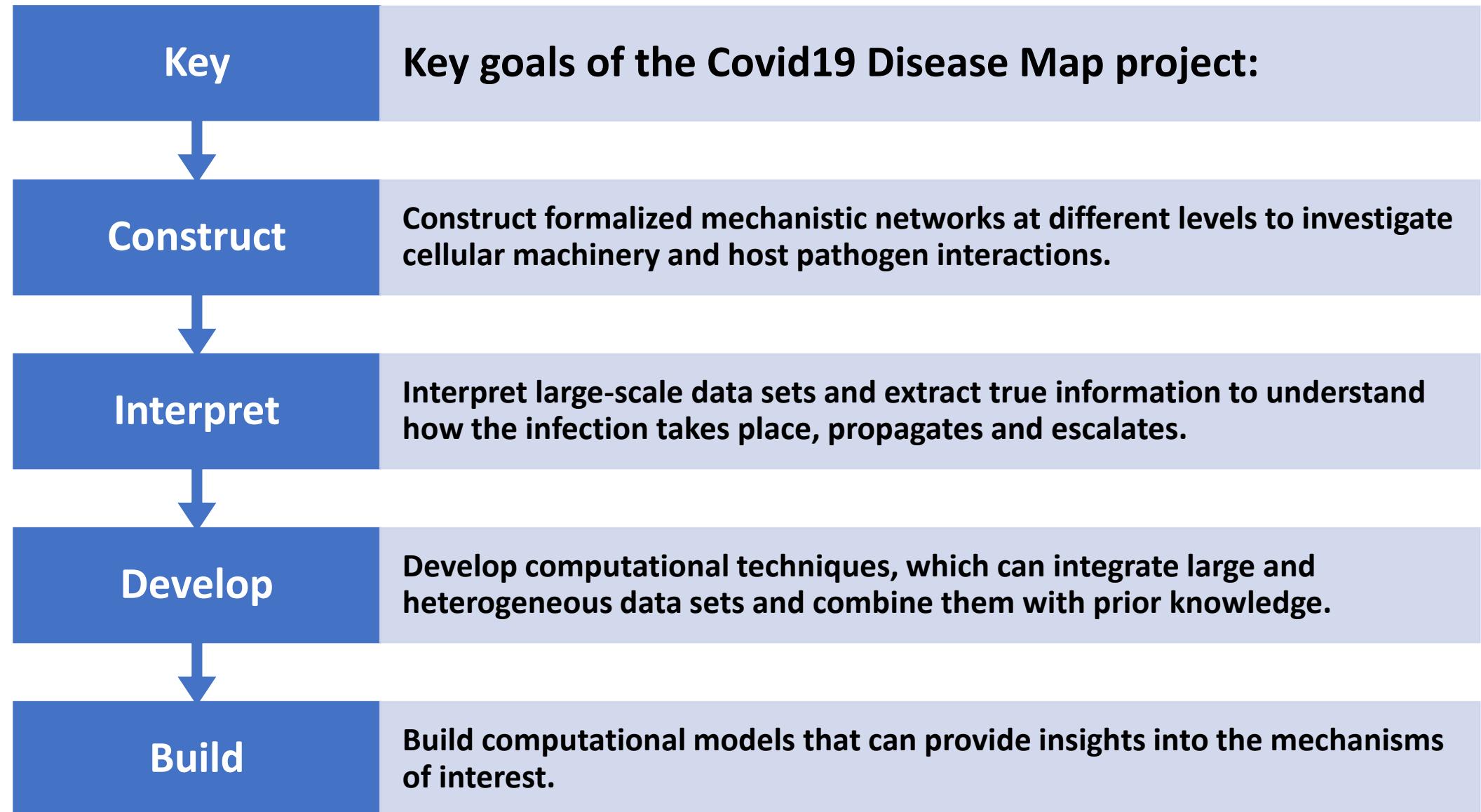


# AI-assisted human biocuration of molecular mechanisms in the COVID-19 Disease Map project

Anna Niarakis\*, John Bachman, Angela Bauch, Benjamin Gyori, Dieter Maier, Marek Ostaszewski

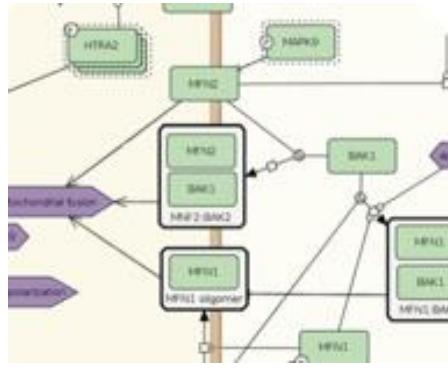
\*Associate Professor,  
UEVE- University of Paris-Saclay, FR  
Lifeware, INRIA Saclay, FR

# A systems biology approach to achieve full scale integration



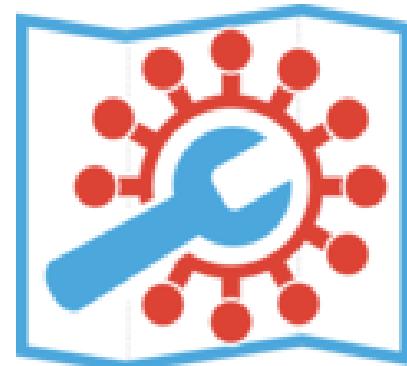
# What do we offer?

- Network encoded disease- specific knowledge
- Templates for Omics data analysis (Molecular, cellular, patient profiles)
- Templates for Drug target data (Drug repurposing)
- Disease Models (Mechanistic insights)



# What do we use?

Literature and information mining  
Human and AI-assisted biocuration  
Systems Biology standards  
Experts' feedback



# The community

## Curation

We share interesting COVID-19 articles using [a Zotero group](#). The group is public-by-invitation to allow file sharing.

Check [curation guidelines](#) to harmonize your content for easier sharing and integration. The guidelines contain information about regular TCs where we discuss our progress.

## Content repositories

**Curated diagrams and code** are shared using [our public Gitlab repository](#).

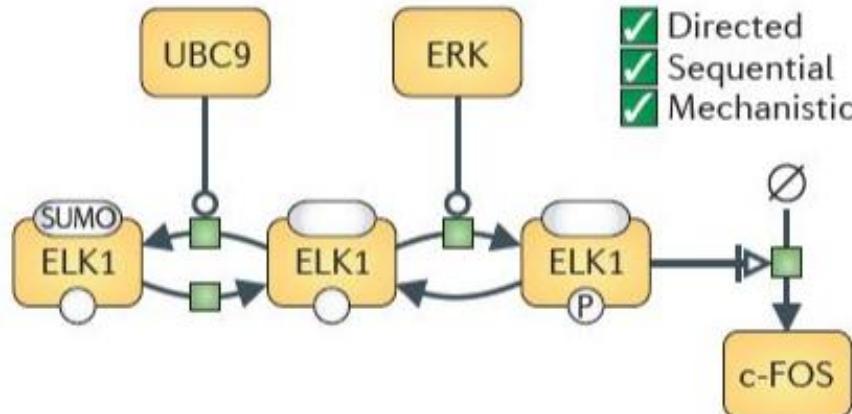
Access with your GitHub login and request developer privileges, or contact [marek.ostaszewski\(at\)uni.lu](mailto:marek.ostaszewski(at)uni.lu).

**WikiPathways** can be shared using [a dedicated collection](#) with COVID-19 related pathways.

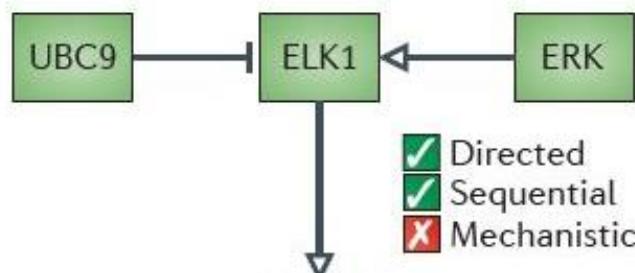
**Reactome** releases [SARS-CoV infections](#) diagrams with mechanisms relevant for COVID-19.

**A weekly build** is available on [the MINERVA Platform](#).

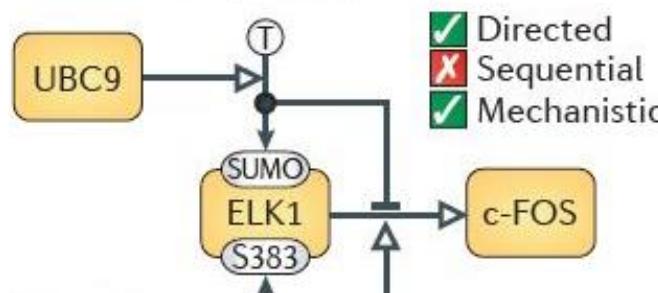
## Process descriptions



## Activity flows



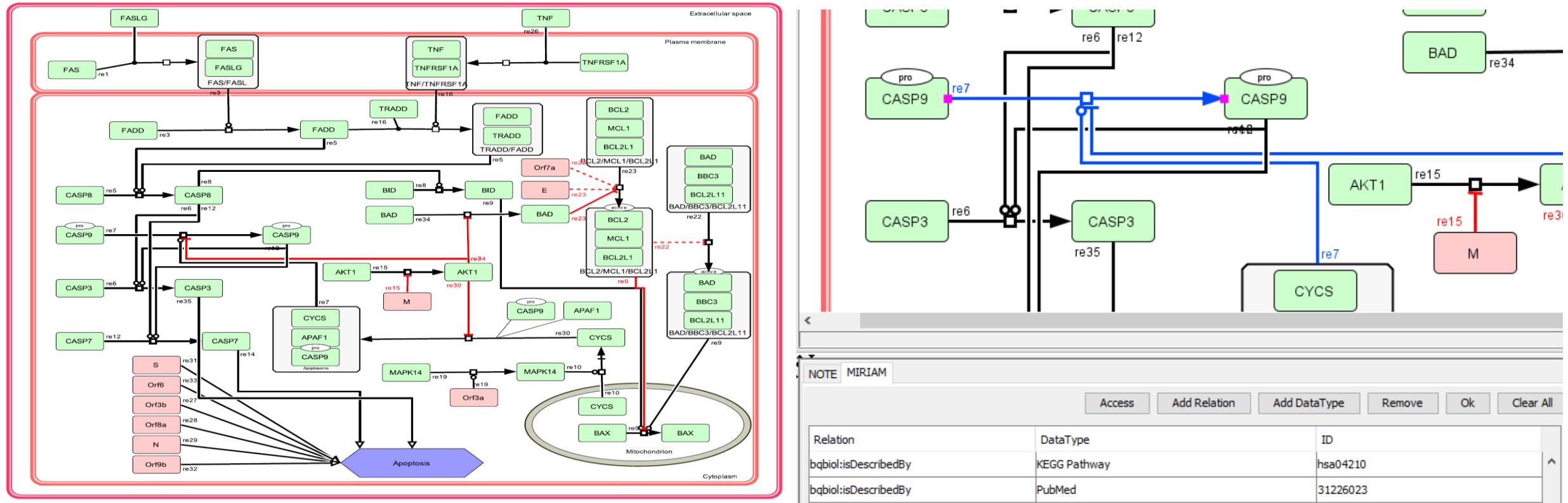
## Entity relationships



# Curation and content sharing using Systems Biology standards

- Independent diagrams content: <git-r3lab.uni.lu/covid/models>
- Visualisation: <covid19map.elixirluxembourg.org>
  - 21 diagrams submitted to date
- WikiPathways COVID19 collection content and visualization: <covid.wikipathways.org>
  - 18 diagrams available
- Reactome SARS-CoV-1 mechanisms content and visualisation: <reactome.org/PathwayBrowser/#/R-HSA-9679506>

# Building diagrams in CellDesigner



## MIRIAM: Minimal Information Required In the Annotation of Models

- Facilitate interoperability and model reusability

# Mechanisms and pathways covered in C19DM

**COVID19 Disease Map**       **04.10.2020**

**SEARCH**   **OVERLAYS**   **SUBMAPS**   **INFO**

**GENERIC**   **DRUG**   **CHEMICAL**   **MiRNA**

**SEARCH:**  
keyword   
PERFECT MATCH

**Reaction:** re979  
**In submap:** Virus replication cycle

**Type:** State transition  
**Annotations:**  
**P:** Source: Annotated by curator  
**A:** [1] [PUBMED \(32047258\)](#)  
[2] [PUBMED \(32142651\)](#)  
[3] [Taxonomy \(2697049\)](#)

**1** Complex: Nucleocapsid  
**In submap:** Virus replication cycle

**Powered by MINERVA Platform (v15.1.0)**

**VIRUS REPLICATION CYCLE**

The diagram illustrates the SARS-CoV-2 Virus Replication Cycle. It begins with the ACE2:SPIKE complex (N2) binding to an EPITHELIAL CELL. Inside the cell, the virus undergoes several stages: 
 

- Initial Stage:** The virus is shown with (+)ss gRNA and oligomer N.
- Intermediate Stage:** The virus contains Orf7a, M, and E proteins.
- Advanced Stage:** The virus contains (+)ss gRNA, oligomer N, and Nucleocapsid.
- Final Stage:** The virus is labeled "exposed HR1-HR2-PP".

 The cycle then moves to the **Kidney, Gastrointestinal, Cardiovascular, Nervous** system, where the virus undergoes **E-RB combination**. 
   
Blue arrows indicate the movement of the virus between stages and its spread to other systems. Numbered circles (1-9) mark specific points of interest along the replication and transmission pathways.

UNIVERSITÉ DU LUXEMBOURG   
LCSB

Kidney, Gastrointestinal, Cardiovascular, Nervous



## Curation and content sharing

Ensure quality and provenance of represented knowledge  
Coordinate parallel efforts



## Integration and interoperability

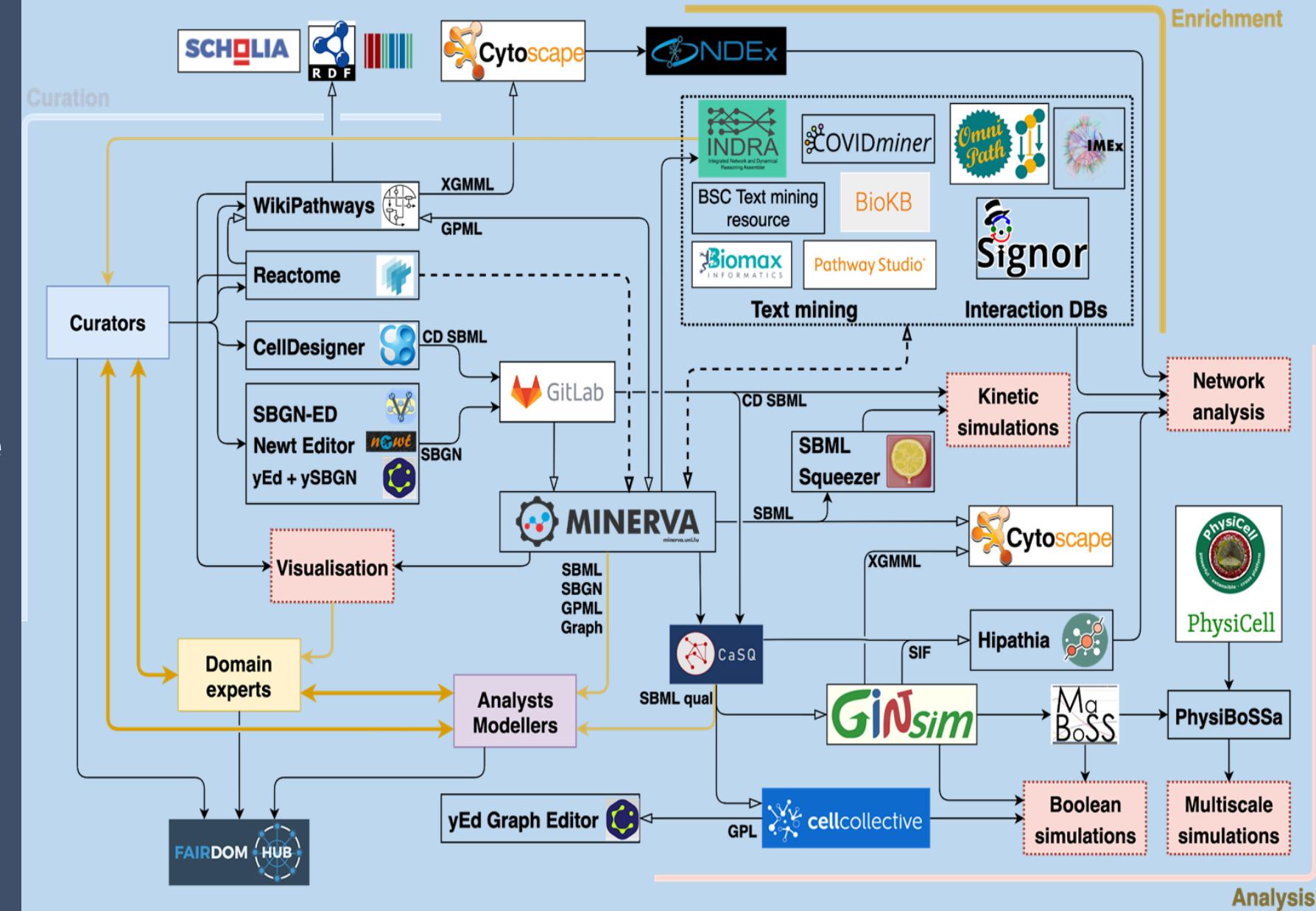
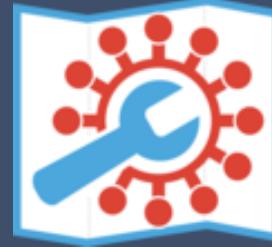
Tools for format interchange  
Enrich the curated content using databases and text mining  
Use AI solutions to enhance and accelerate human curation



## Analysis and Modelling

Use the curated content to produce computational models for prediction and hypothesis generation  
Feedback to the curators

# The Ecosystem of the C19DM project



# First set of curated COVID-19 models

Comment | Open Access | Published: 05 May 2020

## COVID-19 Disease Map, building a computational repository of SARS-CoV-2 virus-host interaction mechanisms

Marek Ostaszewski, Alexander Mazein, Marc E. Gillespie, Inna Kuperstein, Anna Niarakis, Henning Hermjakob, Alexander R. Pico, Egon L. Willighagen, Chris T. Evelo, Jan Hasenauer, Falk Schreiber, Andreas Dräger, Emek Demir, Olaf Wolkenhauer, Laura I. Furlong, Emmanuel Barillot, Joaquin Dopazo, Aurelio Orta-Resendiz, Francesco Messina, Alfonso Valencia, Akira Funahashi, Hiroaki Kitano, Charles Auffray, Rudi Balling & Reinhard Schneider

Scientific Data 7, Article number: 136 (2020) | Cite this article

14k Accesses | 274 Altmetric | Metrics

May 2020

The image shows a screenshot of the bioRxiv preprint server interface. At the top, the bioRxiv logo is displayed along with navigation links for HOME, ABOUT, SUBMIT, NEWS & NOTES, ALERTS / RSS, and CHANNELS. A search bar is present with an advanced search link. A yellow banner at the top of the page states: "bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been peer-reviewed. They should not be regarded as conclusive, practice/health-related behavior, or be reported in news media as established information." Below the banner, the preprint details are shown: "New Results" and "COVID-19 Disease Map, a computational knowledge repository of SARS-CoV-2 virus-host interaction mechanisms". The authors listed are Marek Ostaszewski, Anna Niarakis, Alexander Mazein, Inna Kuperstein, Robert Phair, Aurelio Orta-Resendiz, Vidisha Singh, Sara Sadat Aghamiri, Marcio Luis Acencio, Enrico Glaab, Andreas Ruepp, Gisela Fobo, Corinna Montrone, Barbara Brauner, Goar Frishman, Luis Cristobal Monraz Gomez, Julia Somers, Matti Hoch, Shailendra Kumar Gupta, Julia Scheel, Hanna Borlinghaus, Tobias Czauderna, Falk Schreiber, Arnau Montagud, Miguel Ponce de Leon, Akira Funahashi, Yusuke Hiki, Noriko Hiroi, Takahiro G Yamada, Andreas Dräger, Alina Renz, Muhammad Naveez, Zsolt Bocskei, Francesco Messina, Daniela Bornigen, Liam Ferguson, Marta Conti, Marius Rameil, Vanessa Nakonecnij, Jakob Vanhoefer, Leonard Schmieder, Muying Wang, Emily E Ackerman, Jason E Shoemaker, Jeremy Zucker, Kristin L Oxford, Jeremy Teuton, Ebru Kocakaya, Gokce Yagmur Summak, Kristina Hanspers, Martina Kutmon, Susan Coort, Lars Eijssen, Friederike Ehrhart, Rex D.A.B., Denise Slenter, Marvin Martens, Robin Haw, Bijay Jassal, Lisa Matthews, Marija Orlic-Milacic, Andrea Senff-Ribeiro, Karen Rothfels, Veronica Shamovsky, Ralf Stephan, Cristoffer Sevilla, Thawfeek Mohamed Varusai, Jean-Marie Ravel, Rupsha Fraser, Vera Ortseifen, Silvia Marchesi, Piotr Gawron, Ewa Smula, Laurent Heirendt, Venkata Satagopam, Guanming Wu, Anders Riutta, Martin Golebiewski, Stuart Owen, Carole Goble, Xiaoming Hu, Rupert Overall, Dieter Maier, Angela Bauch, John A Bachman, Benjamin M Gyori, Carlos Vega, Valentin Groues, Miguel Vazquez, Pablo Porras, Luana Licata, Marta Iannuccelli, Francesca Sacco, Denes Turei, Augustin Luna, Ozgun Babur, Sylvain Soliman, Alberto Valdeolivas, Marina Esteban-Medina, Maria Pena-Chilet, Tomas Helikar, Bhanwar Lal Puniya, Anastasia Nesterova, Anton Yuryev, Anita de Waard, Dezo Modos, Agatha Treveil, Marton Laszlo Olbei, Bertrand De Meulder, Aurelien Naldi, Aurelien Dugourd, Vincent Noel, Laurence Calzone, Chris Sander, Emek Demir, Tamas Korcsmaros, Tom C Freeman, Franck Augé, Jacques S Beckmann, Jan Hasenauer, Olaf Wolkenhauer, Egon Willighagen, Alexander R Pico, Chris Evelo, Marc Gillespie, Lincoln D Stein, Henning Hermjakob, Peter D'Eustachio, Julio Saez-Rodriguez, Joaquin Dopazo, Alfonso Valencia, Hiroaki Kitano, Emmanuel Barillot, Charles Auffray, Rudi Balling, Reinhard Schneider, the COVID-19 Disease Map Community. The preprint was posted on October 2, 2020. A blue diagonal banner across the page reads "October 2020". On the right side, there are links for "Comment on this paper", "Previous", "Next", "Download PDF", "Email", "Share", "Supplementary Material", "Citation Tools", "Data/Code", "Tweet", and "Like". A red link "COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv" is also visible. The "Subject Area" section includes "Systems Biology" and "Subject Areas" like "All Articles", "Animal Behavior and Cognition", "Biochemistry", "Bioengineering", "Bioinformatics", "Biophysics", and "Cancer Biology".



# Why do we need AI ?

# Human curation: high-quality but time-consuming, laborious

## PROJECT INFO:

Name: COVID19 Disease Map

Version: 04.10.2020

## Data:

- 624 publication(s)
- [source file](#)
- [EXPORT](#)
- [MANUAL](#)
- Disease: [Betacoronavirus](#)
- Organism: [Homo sapiens](#)

## (sub)map:

<input checked="" type="checkbox"/> Apoptosis pathway	<input checked="" type="checkbox"/> Coagulation pathway	<input checked="" type="checkbox"/> E protein interactions	<input checked="" type="checkbox"/> Electron Transport Chain disruption	<input checked="" type="checkbox"/> Endoplasmatic Reticulum stress
<input checked="" type="checkbox"/> HMOX1 pathway	<input checked="" type="checkbox"/> Interferon 1 pathway	<input checked="" type="checkbox"/> Interferon lambda pathway	<input checked="" type="checkbox"/> JNK pathway	<input checked="" type="checkbox"/> Kynurenine synthesis pathway
<input checked="" type="checkbox"/> Nsp14 and metabolism	<input checked="" type="checkbox"/> Nsp4 and Nsp6 protein interactions	<input checked="" type="checkbox"/> Nsp9 protein interactions	<input checked="" type="checkbox"/> Orf10 Cul2 pathway	<input checked="" type="checkbox"/> Orf3a protein interactions
<input checked="" type="checkbox"/> PAMP signalling	<input checked="" type="checkbox"/> Pyrimidine deprivation	<input checked="" type="checkbox"/> Renin-angiotensin pathway	<input checked="" type="checkbox"/> SARS-CoV-2 RTC and transcription	<input checked="" type="checkbox"/> TGFbeta signalling
<input checked="" type="checkbox"/> Virus replication cycle	<input checked="" type="checkbox"/> overview			

# COVID19 related research

- In the beginning articles were hard to find (diagrams started based on SARS COV1 and other coronaviruses literature)
- Now we are at 10 000 new COVID19 articles per month (!)
- Information overload
- Hard to remain up to date on the latest SARS-CoV-2 and COVID-19 research
- Human brain cannot process all this information
  
- We need to help curators find the information faster
- Give some confidence scores
- Help identify relevant content!
- We need human – machine efficient collaboration

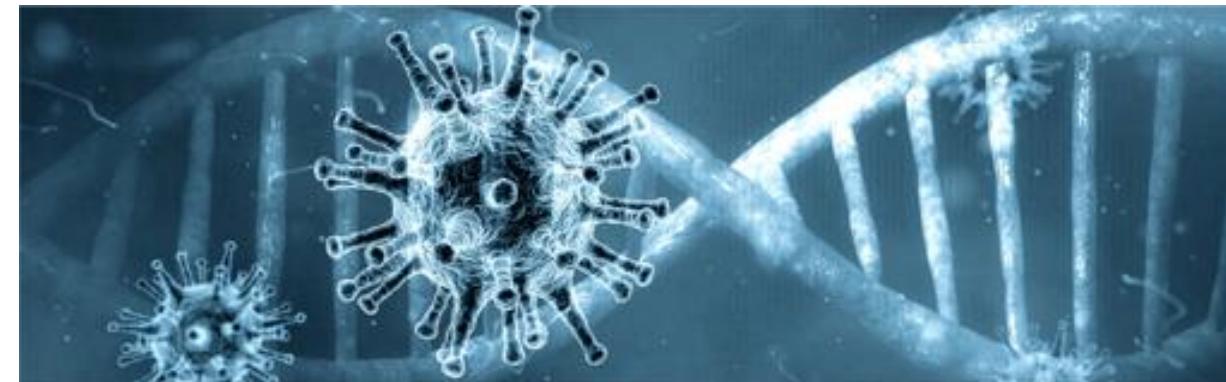
## Literature mining and AI based QA a scientific assistant for COVID-19 research

Dr. Angela Bauch (Assistant Director Product Management)

Dr. Dieter Maier (Director Project Management)

Biomax Informatics AG

<https://ailani.ai>



# AILANI combines two types of algorithms for question answering.

The **natural language processing (NLP)- based literature mining** integrates and continuously mines the resources.

The first approach is based on NLP, parsing the **question into a subject-predicate-object search triple**.

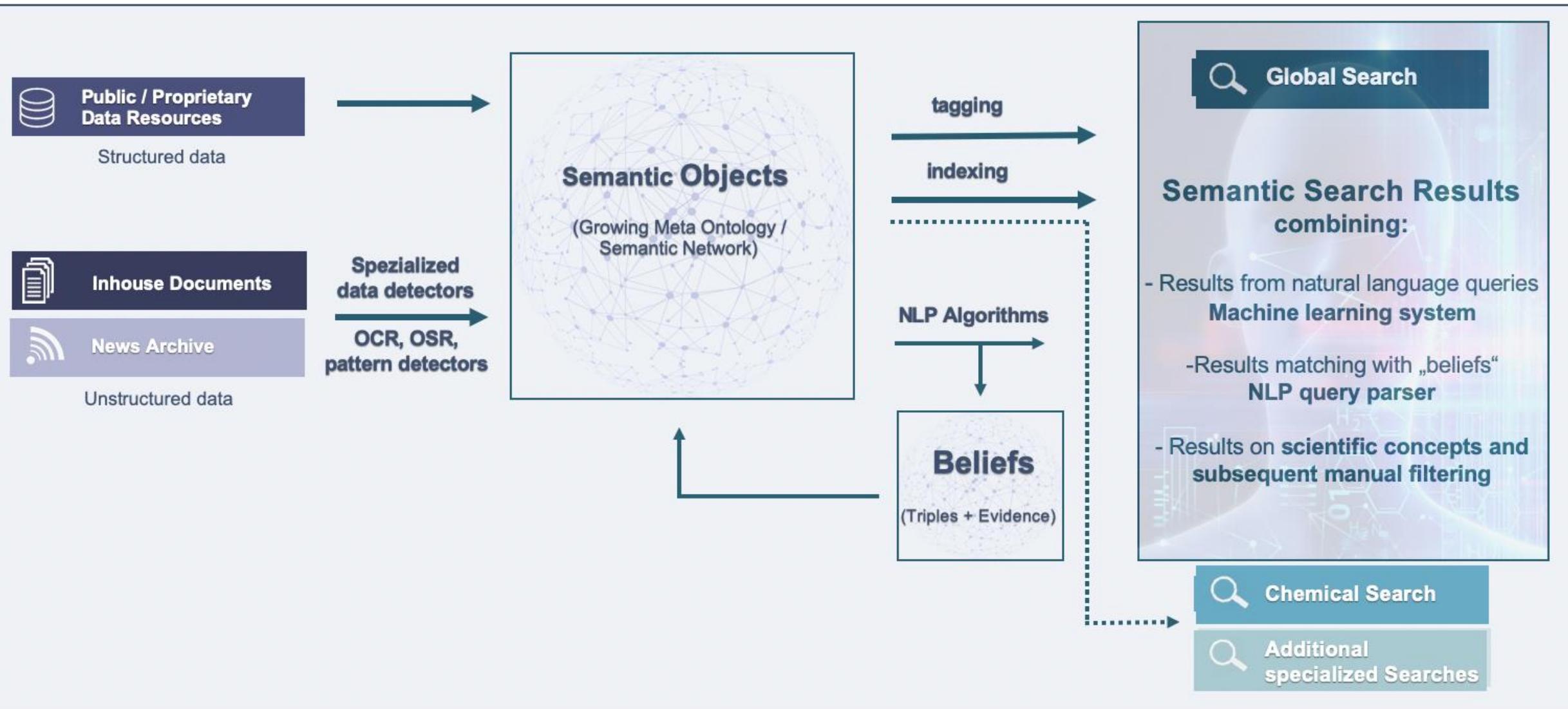
The second approach is based on a **neural network QA algorithm using ontologies for contextualization**, to improve the overall quality and specificity of the ML-generated answers.

**This algorithm identifies objects which are not (yet) part of explicit semantic networks and, therefore, provides novel insights and associations.**

Keyword, phrase and concept search algorithms are utilized within a faceted search interface that offers effective hierarchical drill-down on aggregated representations of the result set.

# Artificial Intelligence (AI) with AILANI

systems  
medicine  
disease  
maps



# Content sources

## > Literature

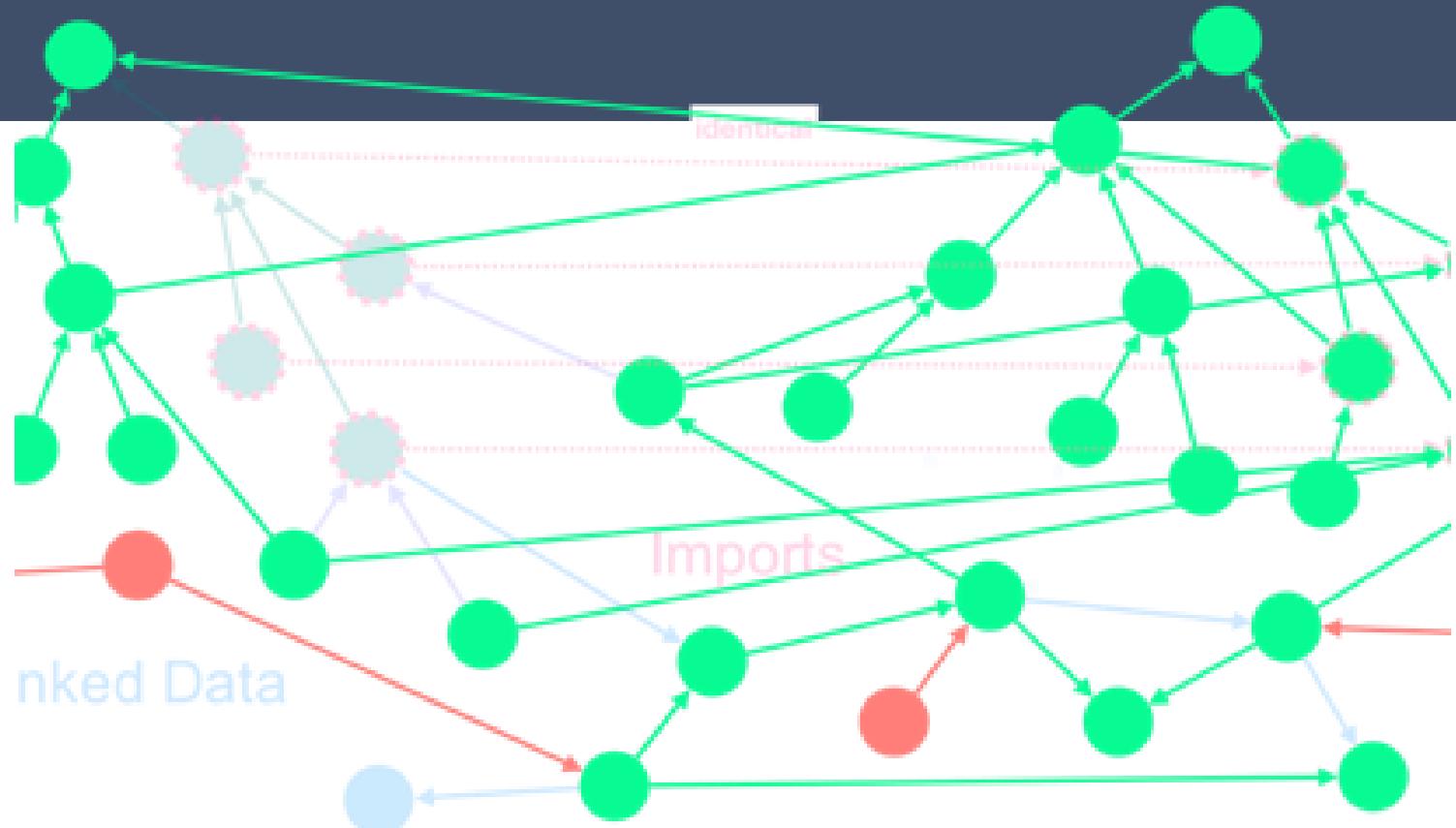
- > Medline abstracts
- > PubMedCentral articles
- > ClinicalTrials.gov
- > COVID-19 lit (Elsevier, medRxiv, bioRxiv)
- > Newsfeeds (WHO, FDA, FoodNav...)
- > COVID-19 patents
- > extendable by proprietary documents (Word, Powerpoint, ELN)

## Databases

- > 70 public databases (UniProtKB, PubChem, ChEMBL, DrugBank, PDB, ICD-10, dbSNP...)
- > *extendable by proprietary structured data (from antibody inventory to chemical library and IP portfolio)*

## > Ontologies

- > 120 life science ontologies (Disease, GO, NCBITax, ChEBI, FMA, HP...)
- > *extendable by proprietary ontologies*



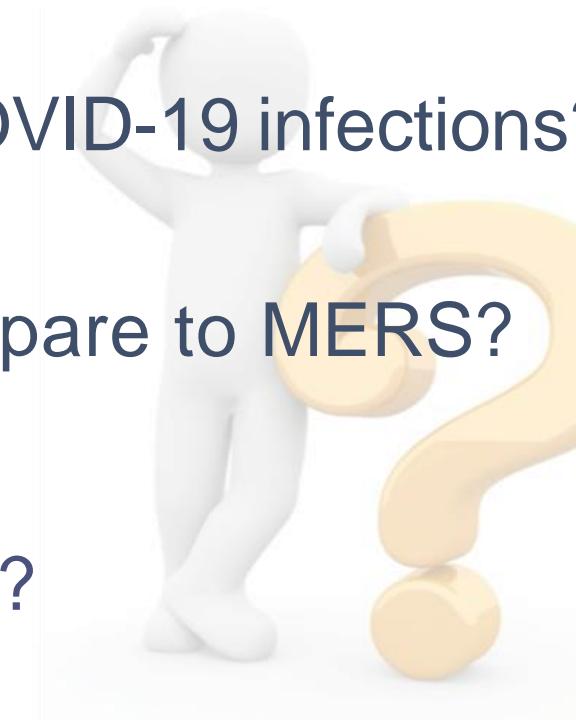
# The Question Answering Index: *Semantic Networks & Neural Networks*

- The AILANI "Hybrid" AI:  
Prior Knowledge, Reasoning  
and Generalization + neural  
networks for bootstrapping a  
"deeper understanding"
- AI: Finding yet unknown  
Concepts...

What does camostat inhibit?

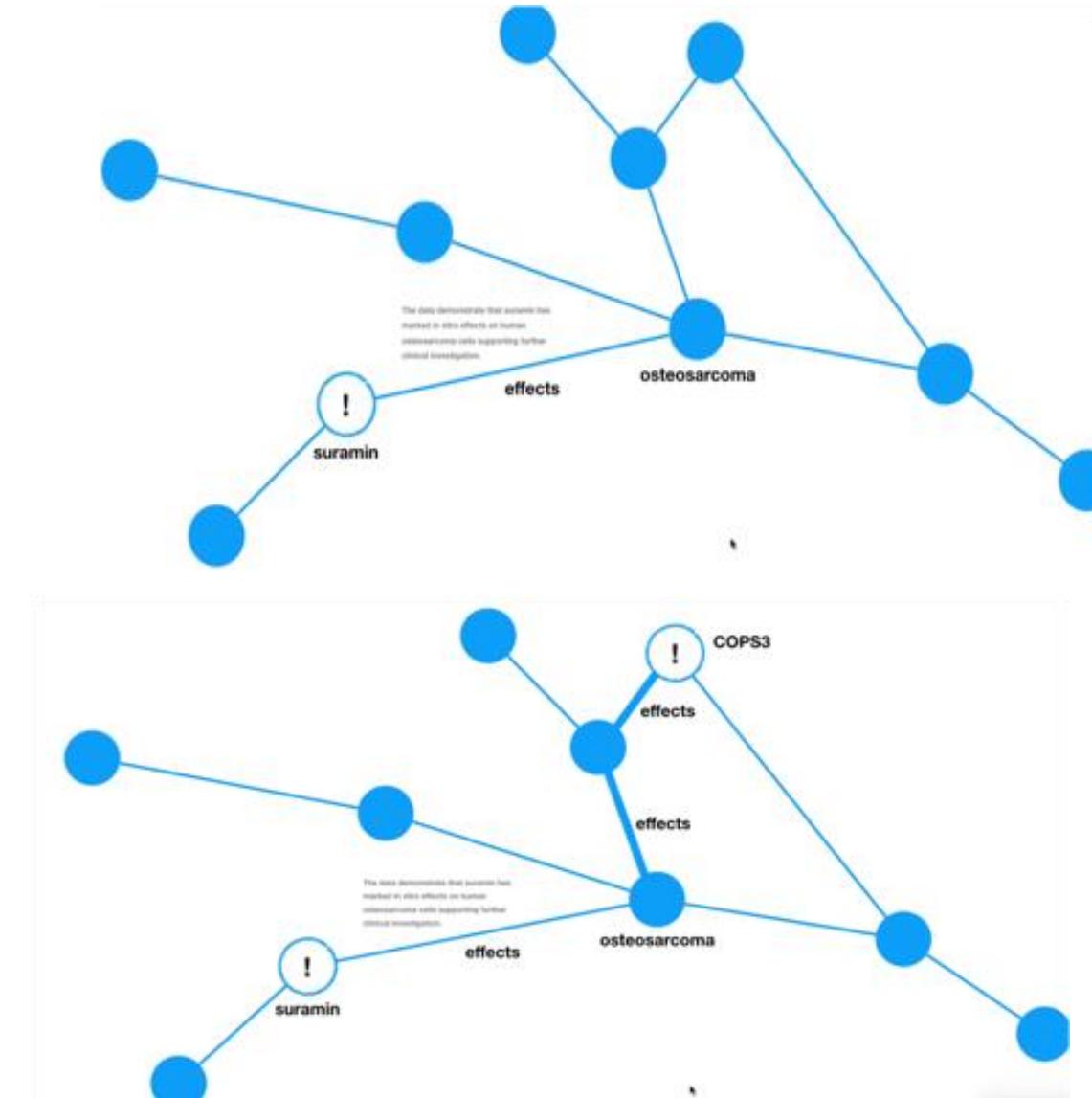
- How to prevent cytokine storms with COVID-19 infections?
  - How does SARS compare to MERS?

How does SARS-CoV enter the cell?



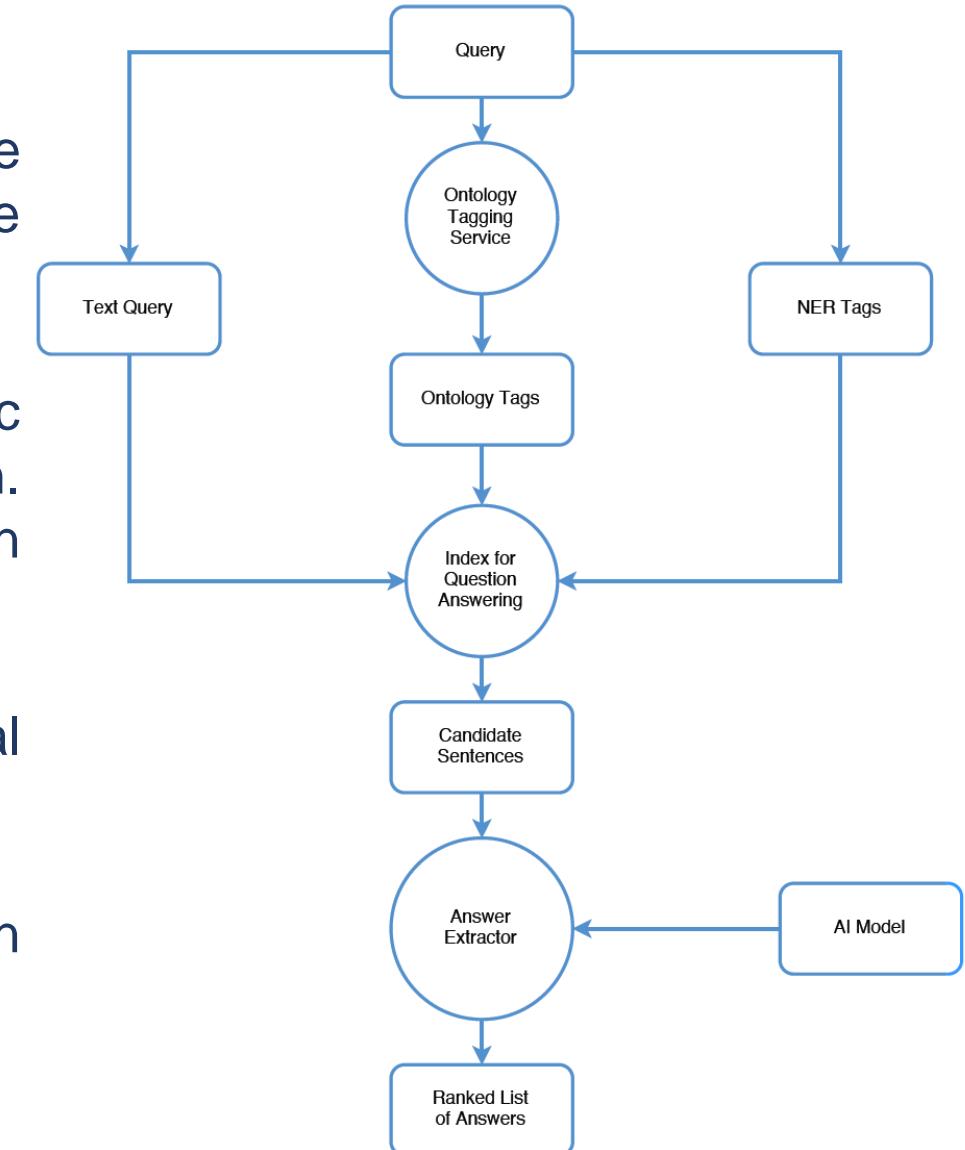
# Semantic Search Algorithms — NLP Question Answering

- > **NLP Parser** — The grammatical structure of an entered natural language question is analyzed
- > **Triple Search** — The entered question is translated into a query against all previously extracted beliefs (triples)
- > **Answer Generator** — The objects of interest encoded in the result triples are reported, including their original source



# Semantic Search Algorithms — AI Question Answering

- > From all documents, a candidate set of 4-sentence chunks is determined, which likely contain possible answers.
- > The candidate set is generated using the semantic tagging index, using ontologies for contextualization. Therefore, the quality of the ontologies has a certain influence on the final answer generated by the AI models.
- > From the candidate set of 4-sentence chunks, a neural network extracts direct answers to the entered question.
- > Based on the ML score, the answers are reported in ranked order.



\*NER: Named Entity Recognition

# Free access to scientists working on COVID19

Home > Search > What are COVID-19 risk factors?

Home  Search  
What are COVID-19 risk factors?



Results found by keywords (13 310)

AI suggestions (18)

Question Answering Combined

Per page: 25 Results: 18 - 

Selected items: 0  Export

## temperature combined with humidity

Our results indicate that **temperature combined with humidity** are risk factors for COVID-19 and Influenza in both climate regimes, and the minimum temperature was also a risk factor for subtropical climate.

Martins, L. D. et al. How socio-economic and atmospheric variables impact COVID-19 and Influenza outbreaks in tropical and subtropical regions of Brazil. *Environ Res* (2020).

 How socio-economic and atmospheric variables impact COVID-19 and Influenza outbreaks in tropical and subtropical regions of Brazil.

## Hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease

temperature combined with humidity

is associated with , ...

 [View Knowledge Graph](#)

[More about this Answer...](#)

Home
Search
What are COVID-19 risk factors
Diseases
cardiovascular system disease
Diseases
COVID-19

Explore Results
1 of 208
Per page: 25
Results: 5,197

Selected items: 0  Export  Add to Favorites

Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System.

Chang, T. S. et al. Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System. *medRxiv* (2020).

Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System. COVID-19 pandemic coupled with phased associated with susceptibility and severity of disease in a diverse population decision making, and prioritize future COVID-19 research. Cardiovascular disease, hypertension, and renal disease were preexisting conditions associated with COVID-19 testing. premorbid risk factors for COVID-19 inpatient admission. Other less established risk factors for COVID-19 inpatient admission. Other less established risk factors for COVID-19 susceptibility and inpatient admission. K

Add to Favorites

COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke.

Belani, P. et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. *medRxiv* (2020).

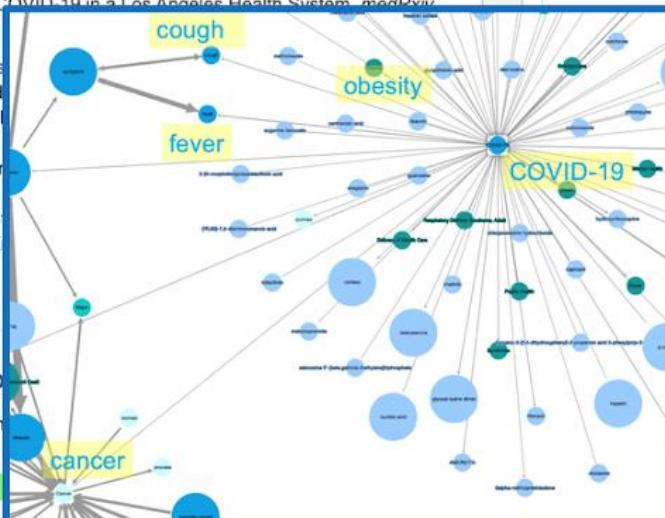
COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. COVID-19 worldwide pandemic with diverse complications. Stroke as a presentation has not been strongly associated with COVID-19. Object: COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. Title: COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. associated with COVID-19. The authors aimed to retrospectively review a lin

Add to Favorites

Risk factors for developing into critical COVID-19.

A multicenter, retrospective, cohort study.

Liu, D. et al. Risk factors for developing into critical COVID-19 patients in Wuhan, China. *medRxiv* (2020).



The Knowledge Graph visualization shows a network of nodes representing concepts. Nodes include 'cough', 'obesity', 'fever', 'COVID-19', 'cancer', and 'hypertension'. Lines represent relationships between these concepts, forming a complex web of associations.

**COVID-19**

is associated with Wuhan seafood market pneumonia virus, Coronaviridae, ...

[View Knowledge Graph](#)

this Concept...

- COVID-19
- COVID-19; ...
- Patents

Filed Mar 31, 2020

nucleic acid detection kit for COVID-19 and use method

Question Answering Combined

Selected items: 0  Export

Hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease

Hypertension, diabetes, COPD, cardiovascular disease, and cerebrovascular disease are major risk factors for patients with COVID-19.

Wang, B., Li, R., Lu, Z. & Huang, Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY)* 12, 6049-6057 (2020).

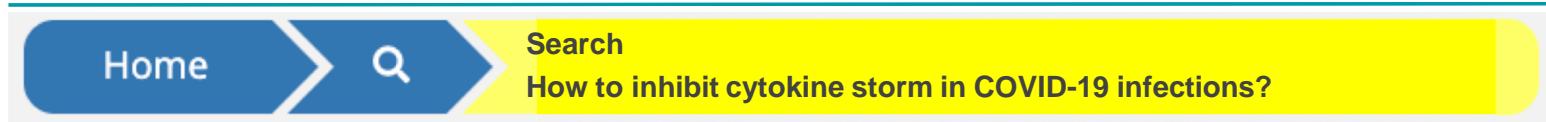
Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis.

temperature combined with humidity

Our results indicate that temperature combined with humidity are risk factors for COVID-19 and Influenza in both climate regimes, and the minimum temperature was also a risk factor for subtropical climate.

How socio-economic and atmospheric variables impact COVID-19 and Influenza outbreaks in tropical and subtropical regions of Brazil

# Ongoing work



## Together with the COVID-19 Disease Map

Collaboration to enrich networks of molecular SARS-CoV-2 infection processes with:

- literature mining evidence
- gene - drug associations
- gene - disease associations
- gene interactions (PPI, transcriptional regulation, miRNA regulation)

### AILANI COVID-19 - a scientific assistant for COVID-19 research

Angela Bauch<sup>1\*</sup>, Martin Wolff<sup>1</sup>, Karsten Wenger<sup>1</sup>, Mariana Mondragón-Palomino<sup>1</sup>, Wenzel Kalus<sup>1</sup>, Anna Niarakis<sup>2,3</sup>, Inna Kuperstein<sup>4</sup>, Marek Ostaszewski<sup>5</sup>, Dieter Maier<sup>1</sup>, Sascha Losko<sup>1</sup>

<sup>1</sup>Biomax Informatics AG, Planegg, Germany

<sup>2</sup>GenHotel, Univ. Évry, University of Paris-Saclay, Genopole, 91025, Évry, France

<sup>3</sup>Lifeware Group, Inria Saclay-Île de France, Palaiseau 91120, France

<sup>4</sup>Institut Curie, PSL Research University, Mines ParisTech, Inserm, Paris, France

<sup>5</sup>Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Belvaux, Luxembourg

# The INDRA Database and Network Search: Comprehensive, context-specific information on biochemical interactions

Dr. John A. Bachman

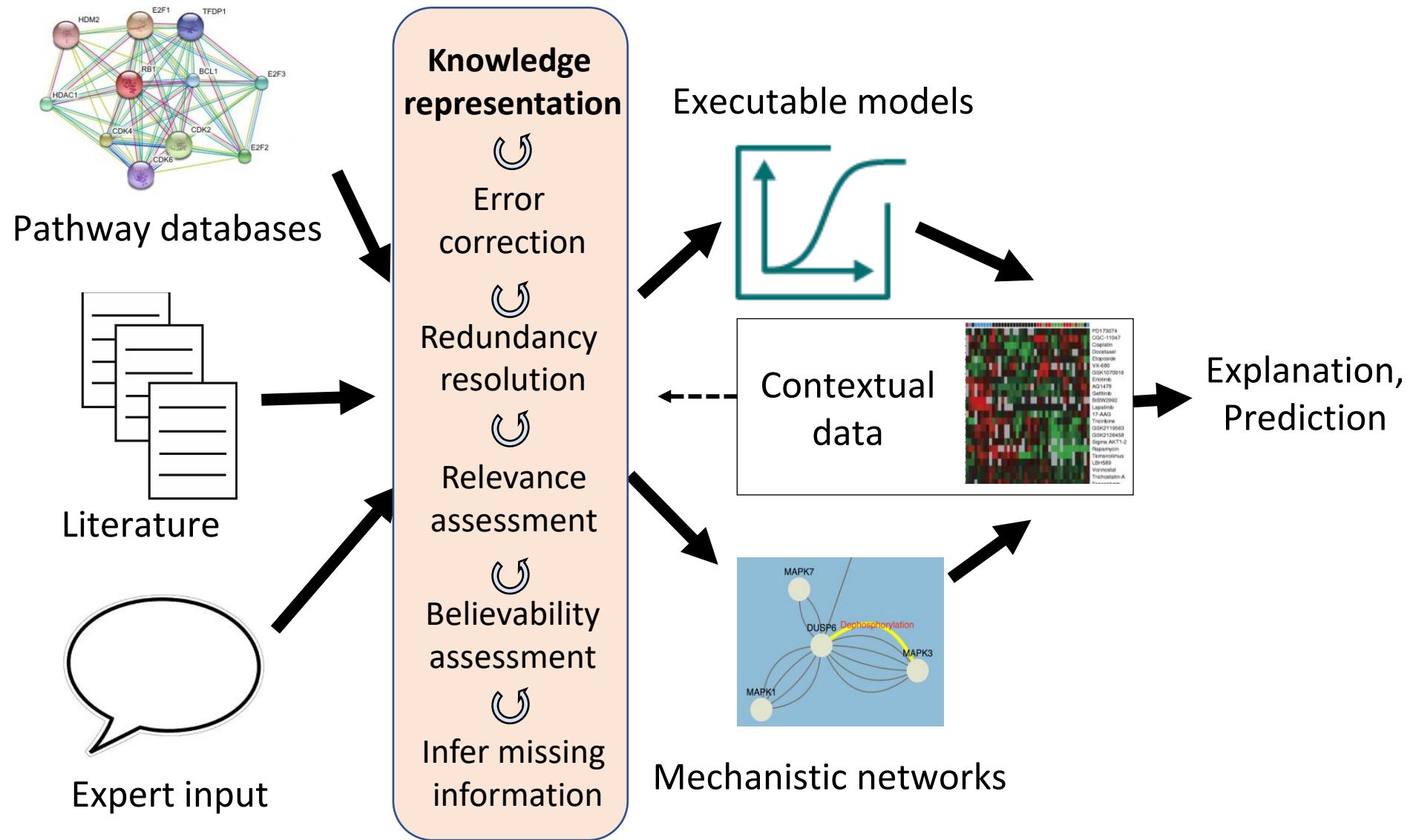
Dr. Benjamin M. Gyori

Laboratory of Systems Pharmacology

Harvard Medical School

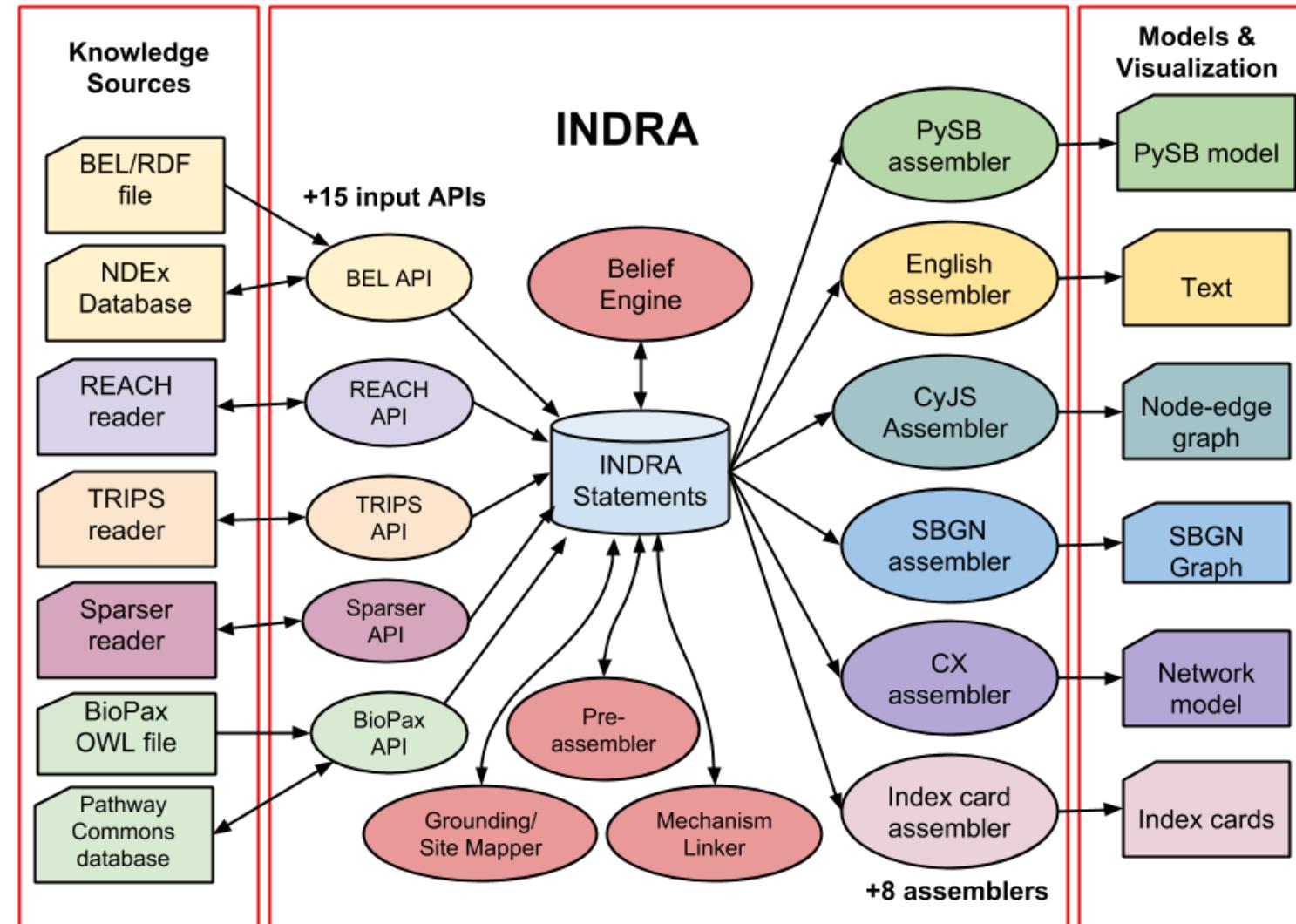


# Conceptual overview of machine-assisted modeling



# INDRA: Integrated Network and Dynamical Reasoning Assembler

systems  
medicine  
disease  
maps



# Reading systems integrated with INDRA

**TRIPS** system: general purpose, deep, semantic reading with domain-specific ontologies

**REACH** system: domain-specific set of patterns used to identify mechanisms in text

**Sparser**: like TRIPS, but takes “greedy” parse, extremely fast (SIFT)

**TEES, Turku Event Extraction System**: SVM-based extraction trained on labeled data

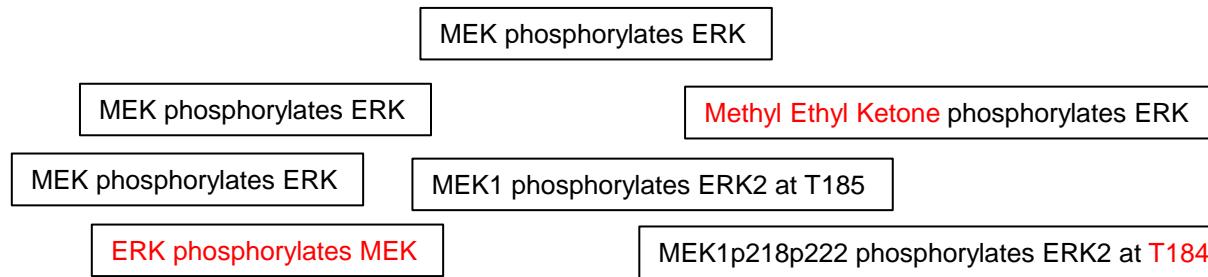
**Medscan**: Elsevier event extraction system.

**Geneways**: Output only. Developed by Andrey Rzhetsky at U. Chicago.

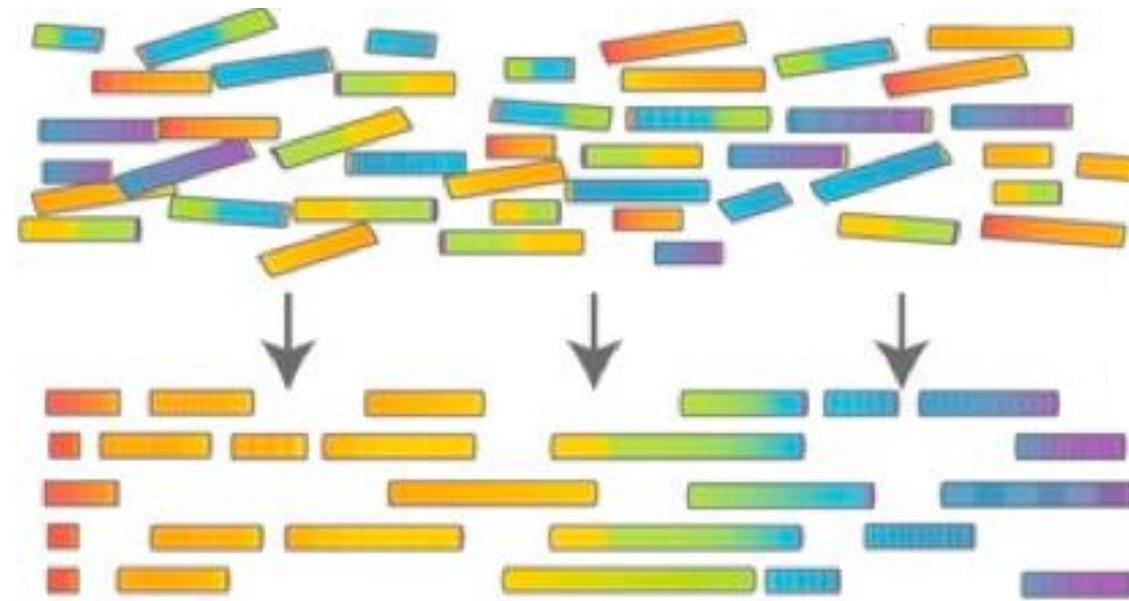
**AMR-based event extraction**: Machine-learning based, developed by USC/ISI.

**RLIMS-P**: U. Delaware text mining system for phosphorylation

# Knowledge assembly is like genome assembly



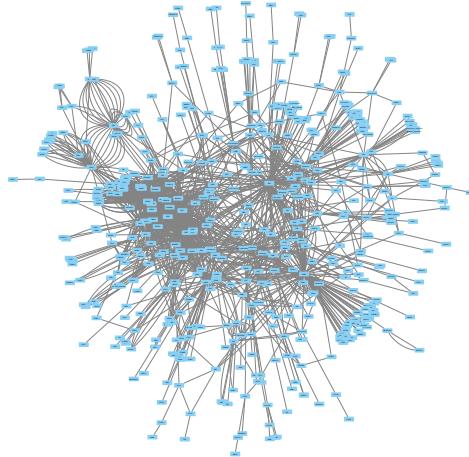
"Raw" mechanisms



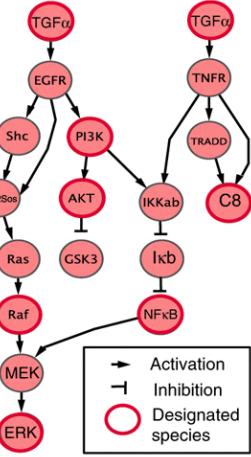
MEK1p218p222 phosphorylates ERK2 at T185.

Assembled mechanisms

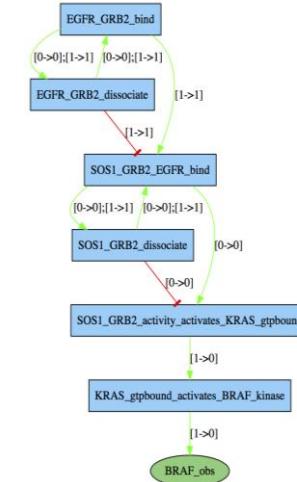
# Mechanistic knowledge can be assembled into different model types



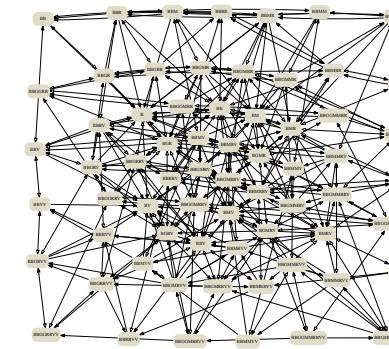
Directed protein interaction graph



Logical network



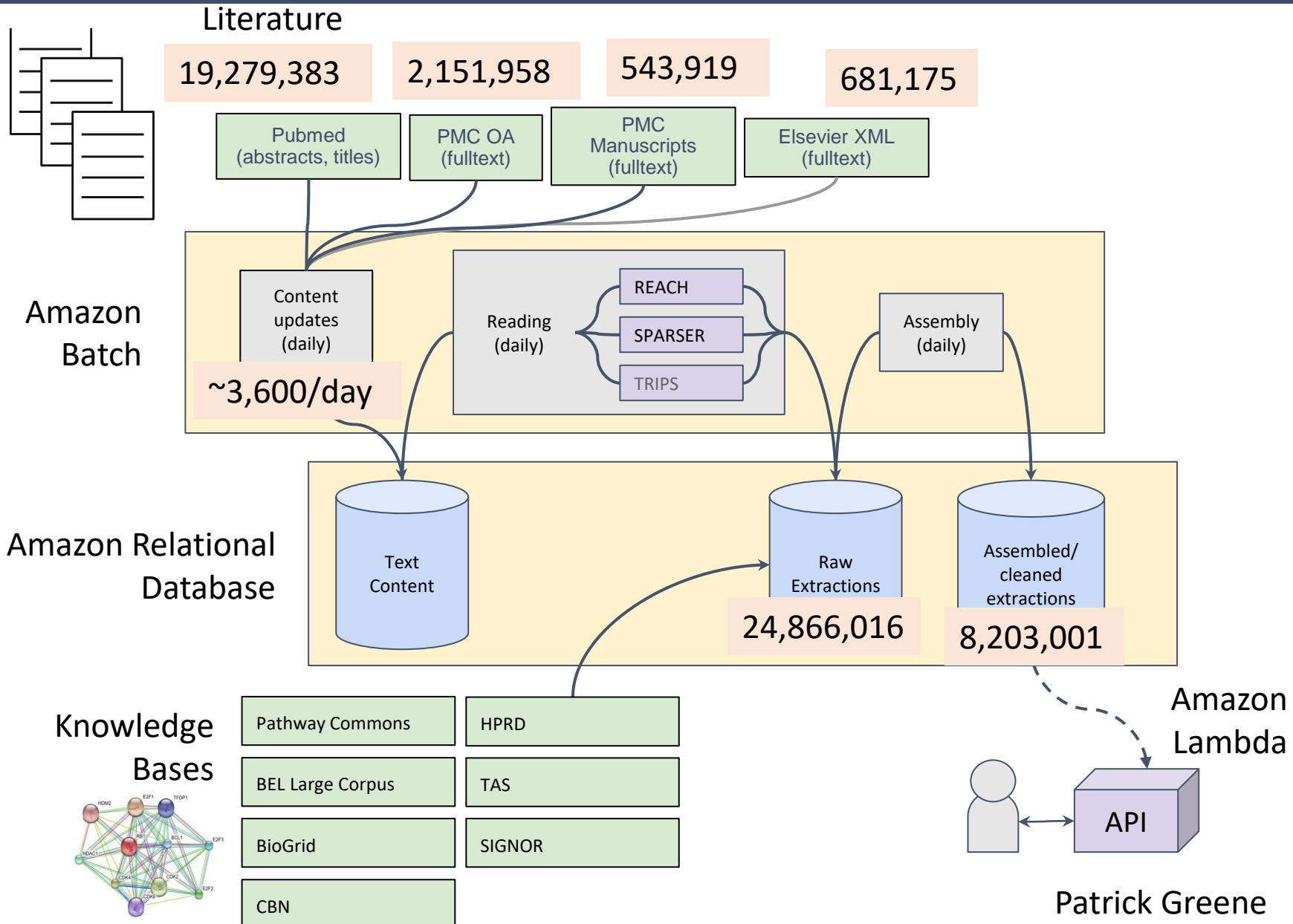
Kappa rule influence map



Chemical reaction network

Mechanistic detail/causal context

# INDRA DB: Keeping up with all biomedical literature



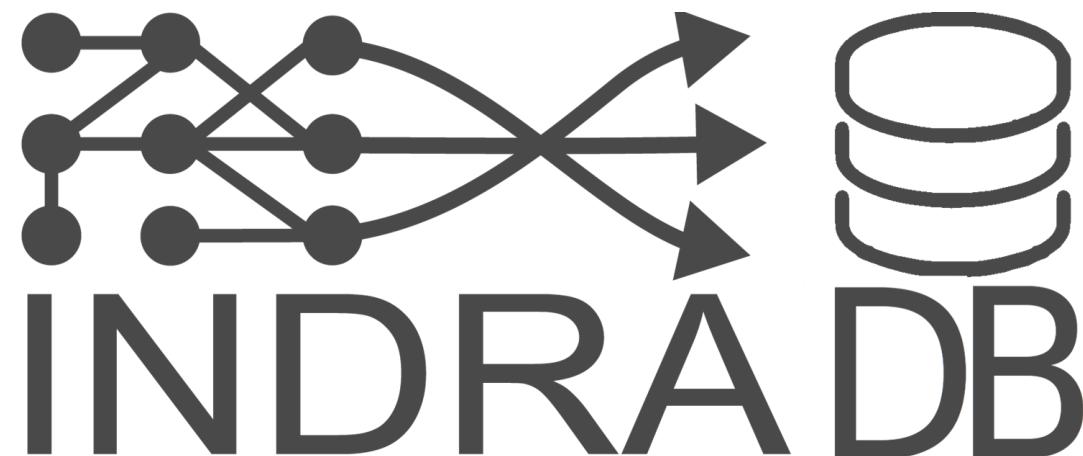
# The INDRA Database

**~20,000** Human  
Proteins

**~1.6 million** Total  
Grounded Entities

**~10 million**  
Unique Interactions

**>3.2 million interactions** among proteins, chemicals, bioprocesses



Continuously  
Updating

Complete  
Provenance Tracking

# The INDRA Database search interface (beta)

systems  
medicine  
disease  
maps

<https://db.indra.bio>

 INDRA Database    Search (Old Search)

## Query Constraints < Back    Forward >

×

**Agent:** role:  text:  namespace:  OR

+

# Adding search constraints

The screenshot shows the INDRA Database search interface at <https://db.indra.bio>. The top navigation bar includes the logo, the text "INDRA Database", and a link to "Search (Old Search)". Below this is the "Query Constraints" section with the following fields:

- Agent: role:  (with a dropdown arrow)
- text:
- namespace:  (with a dropdown arrow)
- OR

Below these fields is a "+ select constraint..." button, which has a dropdown menu open showing the following options:

- agent constraint
- type constraint
- mesh constraint
- paper constraint

A black arrow points from the text "Combine multiple search constraints" down to the "+ select constraint..." button.

- Combine multiple search constraints
- Entities (gene/protein, chemical, bioprocess, etc.)
  - Entity role (subject, object, or either)
  - Relation type (e.g. Activation, Phosphorylation, etc.)
  - Paper (get statements for a specific PMID)
  - MESH term (filter results to papers with MESH IDs)

# Converting search terms into standard identifiers

 INDRA Database   Search (Old Search)   <https://db.indra.bio>

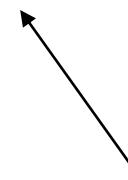
---

Query Constraints < Back   Forward >

Agent: role: any text: **ROS** namespace: auto OR **Ground with GILDA**

+ select constraint...

**Search**



Ambiguous, non-standard name (“ROS”)

# Converting search terms into standard identifiers

The screenshot shows the INDRA Database interface with the URL <https://db.indra.bio>. In the 'Query Constraints' section, there is a dropdown menu for 'Agent: role:' set to 'any'. Below it is another dropdown menu for 'GILDA grounding:' with a placeholder 'Select grounding option...'. A dropdown menu is open, listing four normalization options with their scores and sources:

- ROS1 (score: 1.00, 10261 from HGNC)
- reactive oxygen species (score: 1.00, CHEBI:26523 from CHEBI)
- Rod Cell Outer Segment (score: 0.56, D012374 from MESH)
- Reactive Oxygen Species (score: 0.56, D017382 from MESH)

A blue arrow points from the text 'Alternative normalizations found by GILDA' below to the 'Select grounding option...' dropdown.

## Alternative normalizations found by GILDA

Gilda (<https://github.com/indralab/gilda>, `grounding.indra.bio`) is a Python package and REST service that grounds (i.e., finds appropriate identifiers in namespaces for) named entities in biomedical text. It includes more than ~1,000 machine-learned disambiguation models to choose appropriate senses for ambiguous biomedical entities based on the text context they appear in. It is also very fast, able to ground between 1,000-10,000 strings per second.

# Reviewing evidence, with links to publications

## Results

I found statements that are not only from medscan and have an agent where HGNC=8974 with role=SUBJECT

**PIK3C3 affects BECN1**

2 28 4 | 613 780

**PIK3C3 binds BECN1.**

1 28 4 | 612 766

**PIK3C3 inhibits BECN1.**

| 1 5

**PIK3C3 activates BECN1.**

1 | 6

**PIK3C3 ubiquitinates BECN1.**

| 2

**PIK3C3 ubiquitinates BECN1.**

| 2

reach In contrast, as only samples of cells expressing Ub-Lys 11 showed a ubiquitination pattern comparable with the wild-type Ub, the Lys 11 -linked polyubiquitin chains mediated the enhanced ubiquitination of **Beclin 1** induced by the depletion of **VPS34**.

21936852

reach Polyubiquitinated **BECN1** has an elevated capacity to bind **PIK3C3**, resulting in an enhanced **PIK3C3** kinase activity.  
**PIK3C3 decreases the amount of BECN1.**

24980959

| 1

**PIK3C3 affects PIK3R4**

1 3 1 | 183 152

**ATG14 affects PIK3C3**

1 11 | 166 101

**PIK3C3 affects autophagy**

1 | 3 6 106

**PIK3C3 activates autophagy.**

1 | 2 4 83

**PIK3C3 inhibits autophagy.**

| 1 2 23

**PIK3C3 affects UVRAG**

1 5 | 52 47

**PIK3C3 affects phosphatidylinositol**

| 1 31 69

# Statements can be curated to improve reading over time

## Results

I found statements that are not only from medscan and have an agent where HGNC=8974 with role=SUBJECT

### PIK3C3 affects BECN1

PIK3C3 binds BECN1.

2 28 4 | 613 780

PIK3C3 inhibits BECN1.

1 28 4 | 612 766

PIK3C3 activates BECN1.

1 1 5

PIK3C3 ubiquitinates BECN1.

1 1 6

PIK3C3 ubiquitinates BECN1.

1 2

reach In contrast, as only samples of cells expressing Ub-Lys 11 showed a ubiquitination pattern comparable with the wild-type Ub, the Lys 11 -linked polyubiquitin chains mediated the enhanced ubiquitination of Beclin 1 induced by the depletion of VPS34.

21936852

Select error type...

Optional description (240 chars)

Submit

- Correct
- Entity Boundaries
- Grounding
- No Relation

ed BECN1 has an elevated capacity to bind PIK3C3, resulting in an enhanced PIK3C3 kinase activity.

24980959

- Wrong Relation
- Activity vs. Amount
- Polarity
- Negative Result
- Hypothesis
- Agent Conditions
- Modification Site
- Other...

amount of BECN1.

1 1

- PIK3C3 affects UVRAG

aggy.

1 3 1 | 183 152

aggy.

1 11 | 166 101

aggy.

1 1 3 6 106

aggy.

1 1 2 4 83

aggy.

1 1 2 23

aggy.

1 5 | 52 47

# Context-specific search using MESH terms

INDRA Database Search (Old Search)

---

Query Constraints < Back Forward >

**X Agent:** role: subject GILDA grounding: PIK3C3 (score: 0.50, 8974 from HGNC) **Cancel**

**X Mesh:** GILDA grounding: severe acute respiratory syndrome coronavirus 2 (score: 0.53, C000656484) **Cancel**

**+ select constraint...**

**Search**



Adding a MESH constraint  
("sars-cov-2" normalized to MESH term for SARS-CoV-2 by GILDA)

# Context-specific statements and evidence sentences

## Results

I found statements that are from papers with MeSH ID C000656484, are not only from medscan, and have an agent where HGNC=8974 with role=SUBJECT

**PIK3C3 affects virus growth E6 cells**

**PIK3C3 activates virus growth E6 cells.**

**PIK3C3 activates virus growth E6 cells.**

↳ eidos **VPS34 inhibitors** , Orlistat and Triacsin C inhibited **virus growth in Vero E6 cells** and in the human airway epithelial cell line Calu-3 , acting at a post-entry step in the virus replication cycle .

Load more...

32743584

**PIK3C3 affects severe acute respiratory syndrome coronavirus 2**

**PIK3C3 activates severe acute respiratory syndrome coronavirus 2.**

**PIK3C3 activates severe acute respiratory syndrome coronavirus 2.**

↳ reach Inhibitors of **VPS34** and lipid metabolism suppress **SARS-CoV-2** replication.

32743584

# Direct interactions vs. causal paths

## INDRA Database: Direct interactions

The screenshot shows the INDRA Database search interface. At the top, there is a logo, the text "INDRA Database", and a "Search" button with "(Old Search)" in parentheses. To the right, the URL <https://db.indra.bio> is displayed. Below this, the title "Query Constraints" is followed by navigation links "< Back" and "Forward >". The main search area contains the following fields:

- "Agent: role:" dropdown set to "any", with a "text:" input field "Enter agent here" and a "namespace:" dropdown set to "auto".
- A "Ground with GILDA" button.
- A "+ select constraint..." button.
- A "Search" button.

## INDRA Network Search: Causal paths

The screenshot shows the INDRA Network Search interface. At the top, the title "INDRA Network Search" is displayed, along with the URL <https://network.indra.bio>. Below this, a link "Read the documentation [here](#)." is present. The main search area is titled "Enter search" and includes the following fields:

- "Enter source" input field with a copy icon.
- "Enter target" input field.
- "Path length" dropdown.
- "Max # Paths" dropdown.

# The INDRA Knowledge Network

Represents INDRA preassembled statements as a node-edge digraph, either signed or unsigned

- **Nodes** are represented by agents (~39k nodes: genes/proteins, families/complexes, chemicals, metabolites, biological processes)
- **Edges** are represented by statements (~3.2M edges)
- Agents are associated with namespace and ID
- Edge carries metadata from statement including literature evidence

**IncreaseAmount(SIK3, IL6)**

Type, evidence by source, hash, belief score



SIK3 -> HGNC:29165

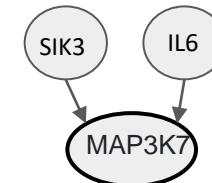
IL6 -> HGNC:6018

# Types of causal queries

- **Paths** between source and target



- **Common targets** directly downstream of source and target



- **Shared regulators** directly upstream of source and target

- **Complexes & Families:** shared complexes and families



- **Open-ended search** either upstream or downstream

# Search interface (alpha)

## INDRA Network Search

Read the documentation [here](#).

### Enter search

TNF

Path length

Enter target

Max # Paths

Allowed node namespaces (does not affect source or target). :

[CHEBI](#) [DOID](#) [EFO](#) [FPLX](#) [GO](#) [HGNC](#) [HP](#)

### Detailed Search Options

*Click to see detailed options*

Download Statements [here](#)

Query resolved! Click [here](#) to download the results as a json

Unweighted vs. weighted

Path length

Node and relation types in paths

Belief score cutoff

Signed vs. unsigned

Node and edge blacklists

Pathway DBs only

**Context-specificity by MESH term**

# Example: why are PTPN11 and EXT1 correlated?

## INDRA Network Search

Read the documentation [here](#).

### Enter search

Path	Weight	Support	Statement types
PTPN11→FGF→EXT1	N/A	<b>PTPN11 → FGF</b> PTPN11, Inhibition, FGF PTPN11, Activation, FGF PTPN11, Dephosphorylation, FGF	Paths: 19 Statement types: 4 reach: 1 medscan: 1 medscan: 1 reach: 11 reach: 1
	N/A	<b>FGF → EXT1</b> FGF, Activation, EXT1	Statement types: 2 reach: 2
PTPN11→STAT5A→EXT1	N/A	<b>PTPN11 → STAT5A</b> PTPN11, Dephosphorylation, STAT5A	Statement types: 2 sparser: 1 reach: 1 hprd: 2
	N/A	<b>STAT5A → EXT1</b> STAT5A, DecreaseAmount, EXT1	Statement types: 2 pc: 1

# Shared regulator search: what inhibits both ACE2 and CTSL?

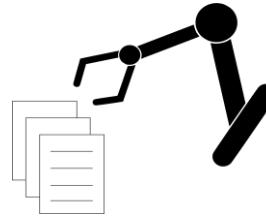
TNF	<b>TNF → ACE2</b>  TNF, IncreaseAmount, ACE2 TNF, Inhibition, ACE2 TNF, Activation, ACE2 TNF, DecreaseAmount, ACE2  <b>TNF → CTSL</b>  TNF, Activation, CTSL TNF, Inhibition, CTSL TNF, IncreaseAmount, CTSL	Support: 5  reach: 2 eidos: 1 reach: 6 reach: 2  Support: 4  reach: 4 reach: 1  medscan: 1 reach: 2
TGFB1	 <b>TGFB1 → ACE2</b>  TGFB1, Activation, ACE2 TGFB1, DecreaseAmount, ACE2 TGFB1, Inhibition, ACE2  <b>TGFB1 → CTSL</b>  TGFB1, Activation, CTSL TGFB1, IncreaseAmount, CTSL TGFB1, DecreaseAmount, CTSL TGFB1, Inhibition, CTSL	Support: 4  reach: 1 reach: 1 reach: 5  Support: 5  reach: 1 reach: 1  medscan: 1 reach: 1 bel_lc: 1 reach: 3

# EMMAA: The Ecosystem of Machine-maintained Models with Automated Analysis



# Automated hypothesis generation from the COVID-19 literature in real time

**1. Extract knowledge when it appears**



**300 new COVID-19 Papers in PubMed each day + preprints!**

**Ecosystem of Machine-maintained Models with Automated Analysis (EMMAA)**

Scientists / Clinicians



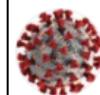
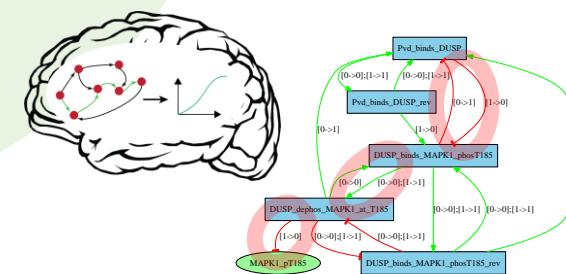
**Queries:**  
Register scientific questions

**Notifications:**  
novel hypotheses,  
analysis reports,

**2. Assemble new knowledge into model**

**EMMAA COVID-19 model** @covid19\_emmaa · 16h  
Today I learned 465 new mechanisms. See [emmaa.indra.bio/dashboard/covi...](http://emmaa.indra.bio/dashboard/covi...) for more details.

**3. Run relevant analysis**



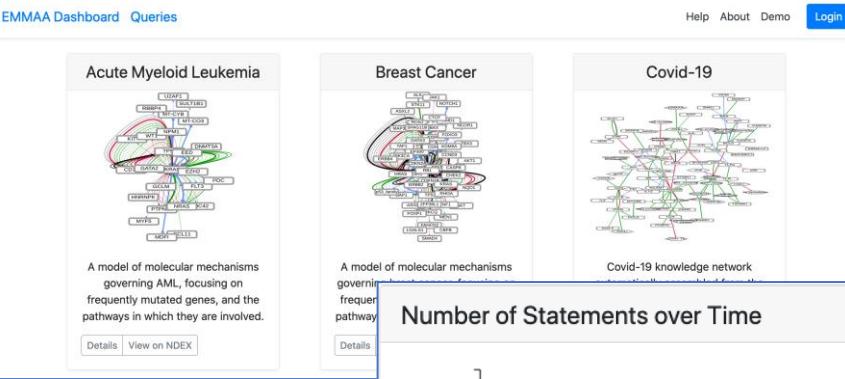
**EMMAA COVID-19 model** @covid19\_emmaa · Oct 4

Today I explained 2 new observations in the MITRE drug-virus effect corpus with my Signed Graph model. See [emmaa.indra.bio/dashboard/covi...](http://emmaa.indra.bio/dashboard/covi...) for more details.

**4. Notify users about novel hypotheses**

# Self-updating and self-testing disease models

EMMAA contains multiple disease and pathway models...

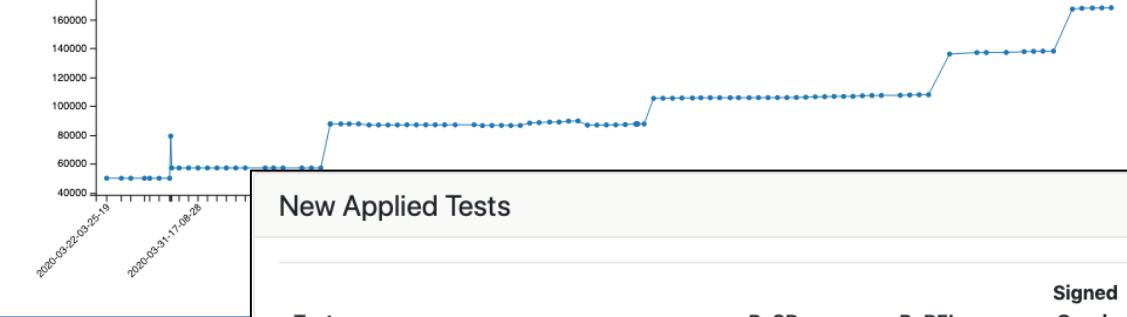


A model of molecular mechanisms governing AML, focusing on frequently mutated genes, and the pathways in which they are involved.

A model of molecular mechanisms governing frequent pathway

Covid-19 knowledge network

**Number of Statements over Time**



2020-03-22, 03-25, 19, 2020-03-31, 17, 04-28

**New Applied Tests**

Test	PySB	PyBEL	Signed Graph	Unsigned Graph
BMP2 activates CASP9.	✗	✓	✓	✓
BMP2 increases the amount of CCND3.	✗	✓	✓	✓
Inflammatory response increases the amount of BMP2.	✗	✗	✗	✗
BMP2 activates MEK.	✗	✓	✓	✓
BMP2 activates p38.	✗	✗	✗	✓

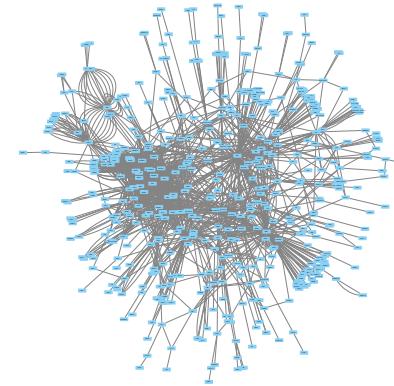
...that evolve over time with new discoveries...

...and are checked for their ability to explain key experimental findings

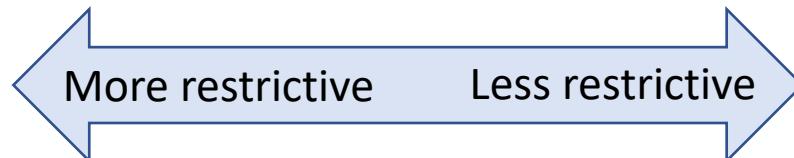
<https://emmaa.indra.bio>

# Models are tested by searching for paths over causal networks

Alternative network representations with different causal constraints allow multi-resolution model-checking



New Applied Tests				
Test	PySB	PyBEL	Signed Graph	Unsigned Graph
BMP2 activates CASP9.	✗	✓	✓	✓
BMP2 increases the amount of CCND3.	✗	✓	✓	✓
Inflammatory response increases the amount of BMP2.	✗	✗	✗	✗
BMP2 activates MEK.	✗	✓	✓	✓
BMP2 activates p38.	✗	✗	✗	✓



# Mechanism of action hypotheses for empirical SARS-CoV-2 inhibitors

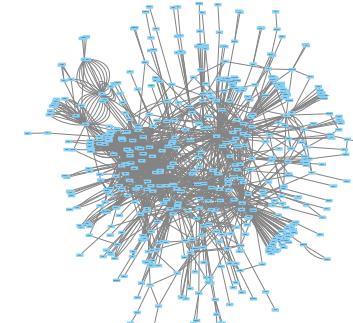
**Question:** how does Proscillaridin inhibit SARS-CoV-2 replication?

**Hypothesis:** Proscillaridin activates AMPK, which activates NFE2L2; NFE2L2 inhibits SARS-CoV-2.

« Previous      Next »

Test: "Proscillaridin inhibits severe acute respiratory syndrome coronavirus 2." for COVID19\_DEV (Signed Graph) on 2020-10-16

Path	Support
Proscillaridin → AMPK → NFE2L2 → severe acute respiratory syndrome coronavirus 2	Proscillaridin → AMPK Proscillaridin activates AMPK. AMPK → NFE2L2 AMPK activates NFE2L2. <b>NFE2L2 → severe acute respiratory syndrome coronavirus 2</b> NFE2L2 inhibits severe acute respiratory syndrome coronavirus 2.



Each step in the pathway is supported by text mined literature evidence...

Statement Evidence and Curation

NFE2L2 inhibits **severe acute respiratory syndrome coronavirus 2.** 31 1/1 JSON

reach This can then be one step when **NRF2** can be modulated to reduce the potential of **SARS-CoV-2** infections in host cells. 32711925

...traceable to source publications.

Trends in Pharmacological Sciences

OPINION | VOLUME 41, ISSUE 9, P598-610, SEPTEMBER 01, 2020

Can Activation of NRF2 Be a Strategy against COVID-19?

Antonio Cuadrado, Marta Pajares, Cristina Benito, ... Gina Manda, Ana I. Rojo, Alibena T. Dinkova-Kostova, Show all authors

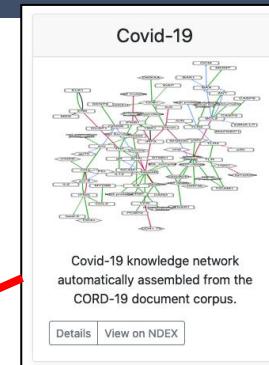
Open Access • Published: July 14, 2020 • DOI: <https://doi.org/10.1016/j.tips.2020.07.003> Check for updates



# Real-time drug repurposing updates

“Open searches” of the causal model to identify *direct or indirect* regulators of a protein, process, phenotype or disease

Users get updated query results by email



Example email update from the EMMAA COVID-19 model:

**Updates to your [open queries](#)**

- "What inhibits COVID-19? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Unsigned Graph model type. For details click [here](#).
- "What inhibits TMPRSS2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Signed Graph model type. For details click [here](#).
- "What inhibits TMPRSS2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using the Unsigned Graph model type. For details click [here](#).
- "What inhibits COVID-19? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using
- "What inhibits ACE2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using
- "What inhibits ACE2? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using
- "What inhibits Middle East Respiratory Syndrome Coronavirus? (CHEBI, DRUGBANK,
- "What inhibits Middle East Respiratory Syndrome Coronavirus? (CHEBI, DRUGBANK,
- "What does leupeptin inhibit? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using
- "What does leupeptin inhibit? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using
- "What inhibits CTSB? (CHEBI, DRUGBANK, CHEMBL, PUBCHEM)" in covid19 using

losartan → ACE2 → COVID-19      losartan → ACE2

Losartan activates ACE2.  
Losartan increases the amount of ACE2.  
Losartan deubiquitinates ACE2.

ACE2 → COVID-19  
ACE2 inhibits COVID-19.  
ACE2 binds COVID-19.  
ACE2 increases the amount of COVID-19.  
ACE2 activates COVID-19.  
COVID-19 binds ACE2.

pioglitazone → ACE2 → COVID-19      pioglitazone → ACE2

Pioglitazone activates ACE2.  
Pioglitazone increases the amount of ACE2.  
Pioglitazone decreases the amount of ACE2.  
Pioglitazone inhibits ACE2.

ACE2 → COVID-19  
ACE2 inhibits COVID-19.  
ACE2 binds COVID-19.  
ACE2 increases the amount of COVID-19.  
ACE2 activates COVID-19.  
COVID-19 binds ACE2.

Med Hypotheses. 2020 Jul; 140: 109776.  
Published online 2020 Apr 22. doi: [10.1016/j.mehy.2020.109776](https://doi.org/10.1016/j.mehy.2020.109776)

PMCID: PMC7175844  
PMID: 32344313

Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19?  
Elena Carboni,<sup>b</sup> Anna R. Carta,<sup>a</sup> and Ezio Carboni<sup>a,\*</sup>

New mechanistic discoveries highlight new therapeutic opportunities

# Incorporating curated COVID-19 models

Comment | [Open Access](#) | Published: 05 May 2020

## **COVID-19 Disease Map, building a computational repository of SARS-CoV-2 virus-host interaction mechanisms**

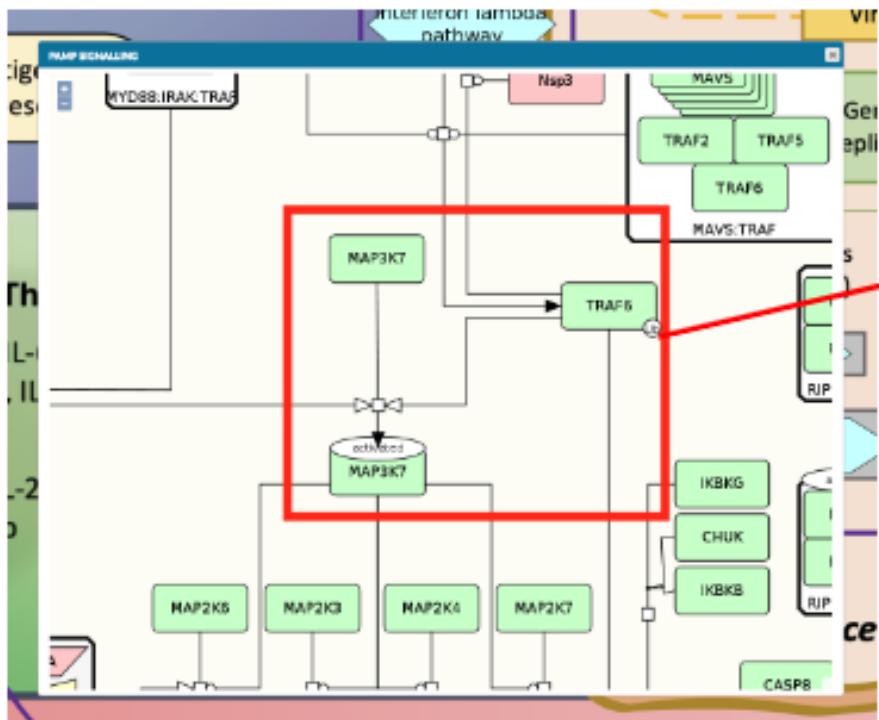
Marek Ostaszewski, Alexander Mazein, Marc E. Gillespie, Inna Kuperstein, Anna Niarakis, Henning Hermjakob, Alexander R. Pico, Egon L. Willighagen, Chris T. Evelo, Jan Hasenauer, Falk Schreiber, Andreas Dräger, Emek Demir, Olaf Wolkenhauer, Laura I. Furlong, Emmanuel Barillot, Joaquin Dopazo, Aurelio Ortega-Resendiz, Francesco Messina, Alfonso Valencia, Akira Funahashi, Hiroaki Kitano, Charles Auffray, Rudi Balling & Reinhard Schneider 

[Scientific Data](#) 7, Article number: 136 (2020) | [Cite this article](#)

**14k** Accesses | **274** Altmetric | [Metrics](#)

21 models of host-virus interactions and disease-relevant pathways

## Alignment with the COVID-19 Disease Map



251 evidences found for this reaction by INDRA

TRAF6 activates MAP3K7.

- |           | Evidence Description   | ID       |
|-----------|--|----------|
| % sparser | It was also shown that ubiquitinated <b>TRAF6</b> activates the <b>TAK1</b> complex to phosphorylate the IKK complex directly.   | 12106781 |
| % reach   | Shortly, TLR4 homodimerization recruits MYD88 and the IRAK complex including <b>TRAF6</b> that activates <b>TAK1</b> .   | 29438282 |
| % sparser | The activated IRAK family proteins associate with <b>TRAF6</b> (TNF receptor-associated factor 6), and <b>TRAF6</b> activates <b>TAK1</b> , which in turn activates the IKK complex composed of NEMO, IKK $\alpha$ and IKK $\beta$ .     | 26309029 |
| % sparser | It was previously shown that <b>TRAF6</b> and <b>RIP1</b> can activate <b>TAK1</b> and lead to IKK phosphorylation and activation ( xref , xref ).   | 21911455 |
| % sparser | The IRAK1- <b>TRAF6</b> complex then activates <b>TAK1</b> through a process involving cytosol translocation of <b>TAK1</b> and two regulatory components TAB-binding protein 2 (TAB2) and TAB3 and the ubiquitination of <b>TRAF6</b> . | 21977329 |

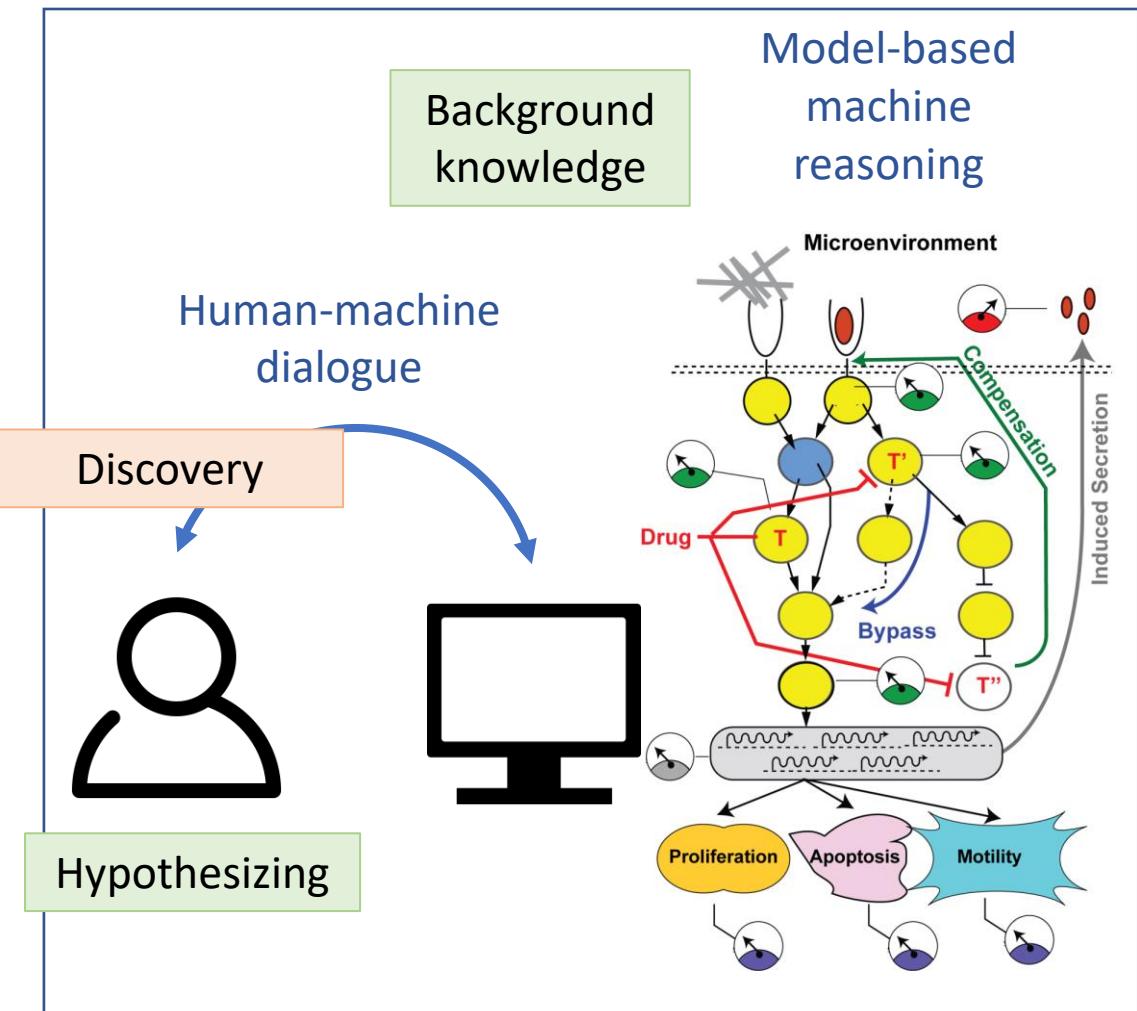
Full alignment (available through [covid19.indra.bio](https://covid19.indra.bio)):

- 656,418 INDRA Statements that contain *at least one* of the COVID-19 Disease Map entities
- 40,361 INDRA Statements whose entities are *all* in the COVID-19 Disease Map

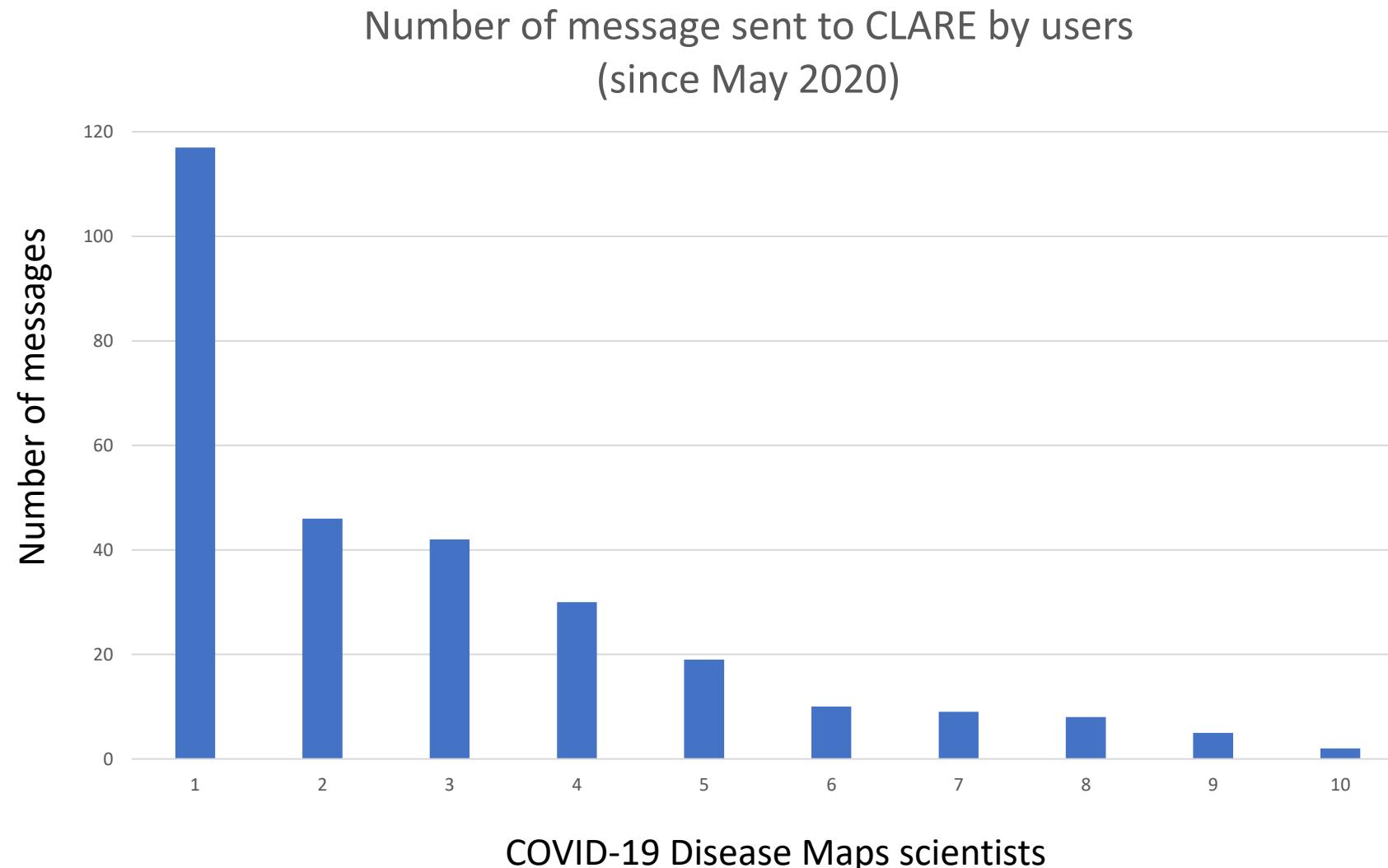
# The CLARE bot in Slack



## Collaborative problem solving

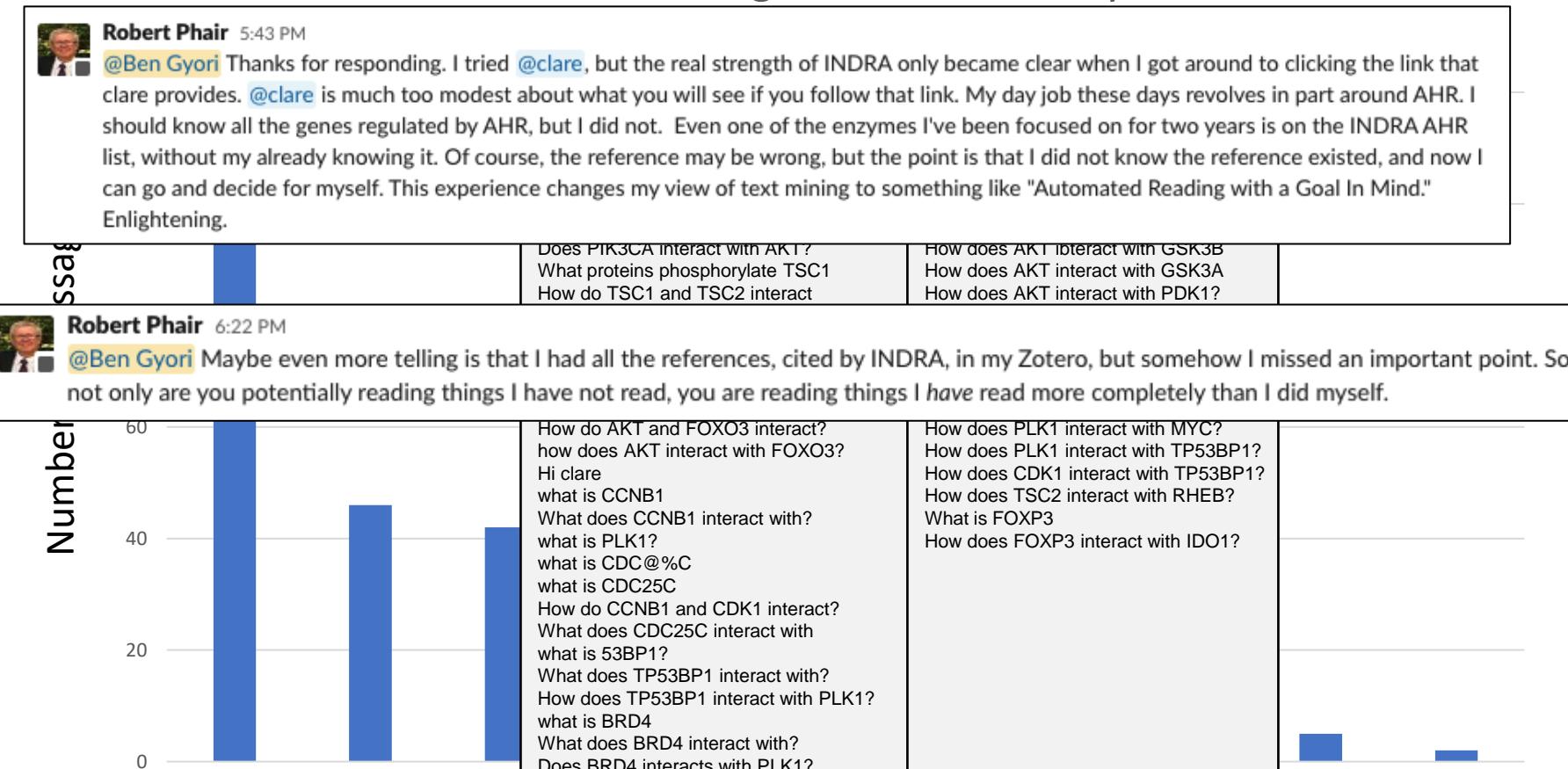


# Usage within the COVID-19 Disease Maps community



# Usage within the COVID-19 Disease Maps community

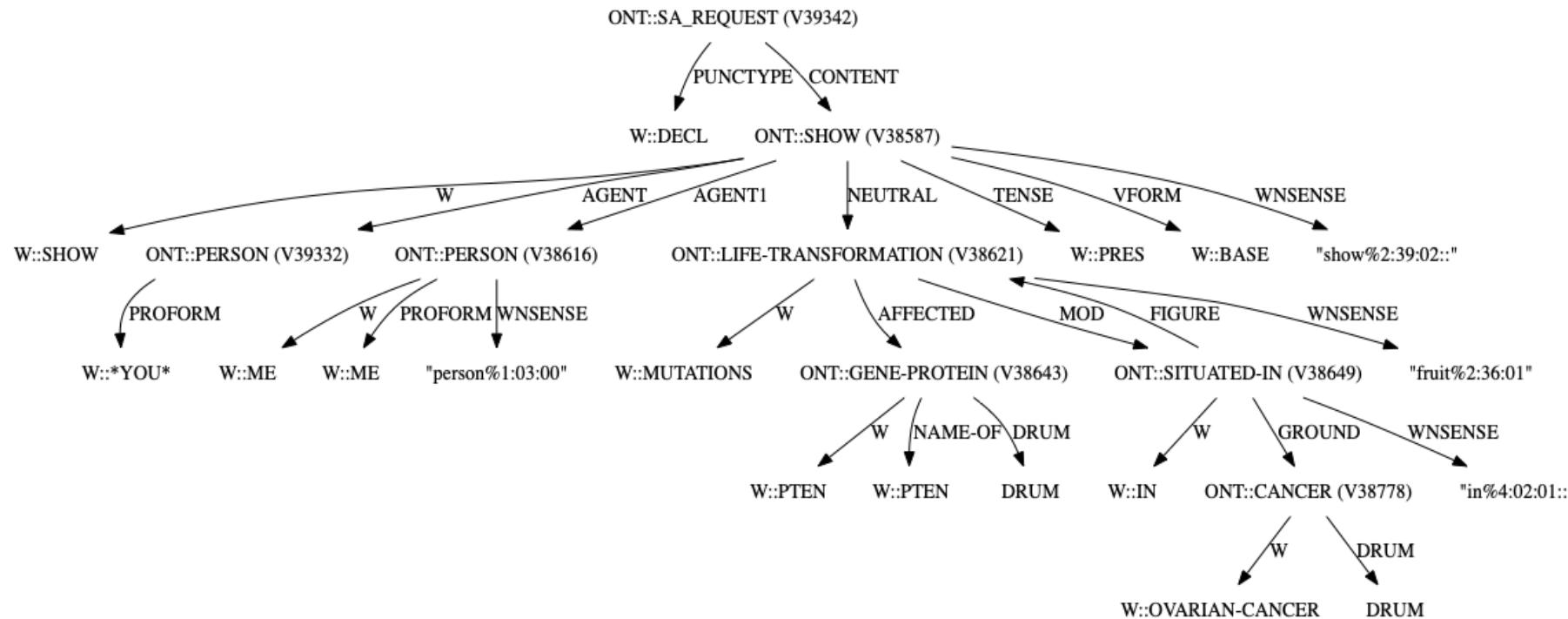
## Number of message sent to CLARE by users



We also got 81 INDRA Statement curations from outside users!

# Challenge in connecting NL with back-end capabilities

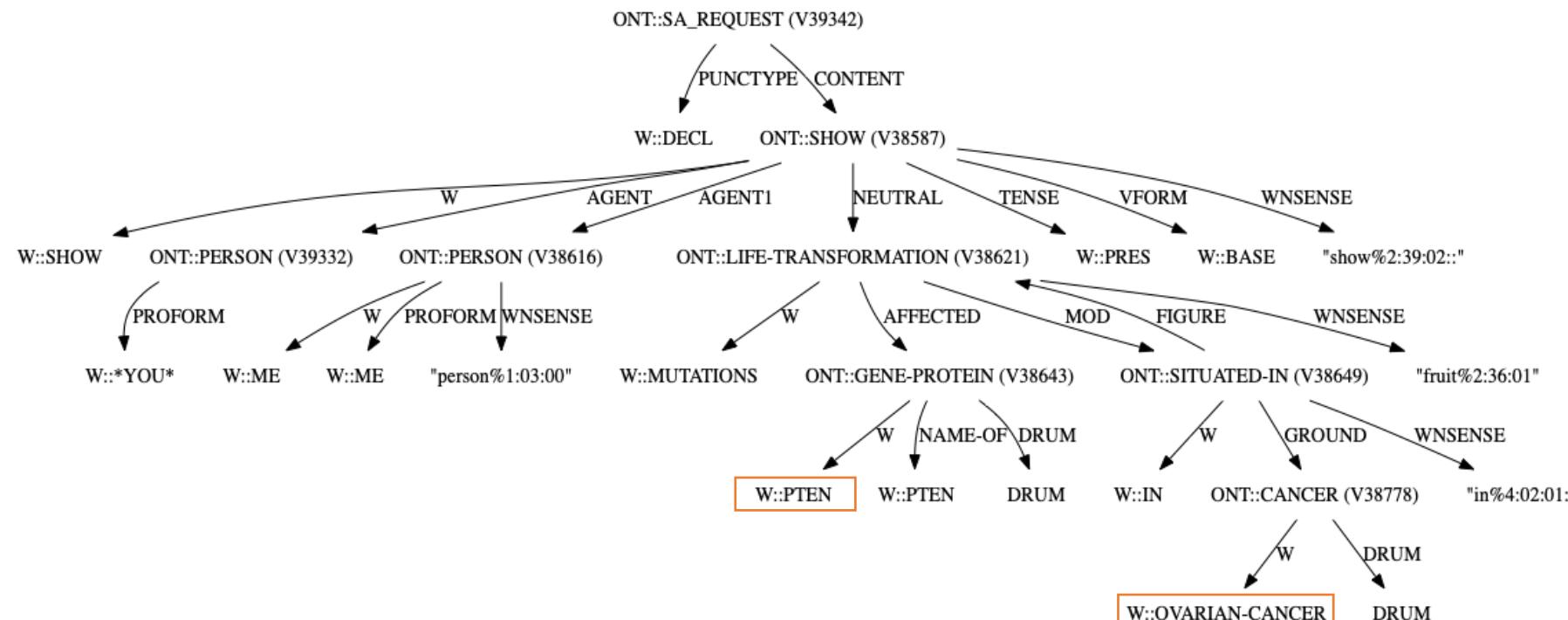
## Variability in language - variability in representation



"Show me mutations of PTEN in ovarian cancer"

Engineering and re-engineering patterns to match interpretations: one of the most time-consuming activities during the project!

# Learning by example



“Show me mutations of PTEN in ovarian cancer”

AutoPattern: given the annotated example, finds the annotated nodes and learns the semantic constraints over their induced subgraph

## Advantages

- Independent of type of reading system (dependency graph, interpretation graph, etc.)
  - Independent of the state of the reading system (robust to changes in graph structure)
  - Intuitive to define, doesn't require coding

# AutoPattern examples

```
"GetSynonyms": [  
  {  
    "text": "what are some other names for AKT1?",  
    "objects": {  
      "AKT1": {  
        "name": "agent",  
        "extract_as": "agent",  
        "match_as": "molecule"  
      }  
    }  
  },  
]
```

- Simple JSON Schema for defining patterns
- Separated from code into standalone resource file (patterns.json) – can be edited without coding

```
{  
  "text": "Show me the mutations of PTEN in ovarian cancer?",  
  "objects": {  
    "PTEN": {  
      "name": "gene",  
      "extract_as": "agent",  
      "match_as": "protein"  
    },  
    "ovarian cancer": {  
      "name": "disease",  
      "extract_as": "ekb",  
      "match_as": null  
    }  
  }  
}
```

# Teaching the system during runtime

 **bgyori** 10:11 AM  
okay, so I can show a few examples

**@clare** which compound's target is BRAF?

 **clare** APP 10:11 AM  
Sorry, I'm not sure what that means.

 **bgyori** 10:11 AM  
^ this is an example of something that I know there is a working capability for but CLARE doesn't understand the language here  
so I can now define an AutoPattern for that capability with this example sentence and some object annotations

**@clare** AutoPattern: FindTargetDrug "which compound's target is BRAF?" compound:None BRAF:target|match:protein|extract:agent

 **clare** APP 10:12 AM  
Alright, I added an AutoPattern.

 **bgyori** 10:12 AM  
so you see FindTargetDrug is the name of the capability, after that, I give the example sentence, and finally, I annotate some words in the example sentence

**@clare** which compound's target is MAP2K1?

 **clare** APP 10:13 AM  
I know that Neratinib, PD184352, Selumetinib, PD0325901, Staurosporine, Trametinib, Nintedanib, Foretinib, AZD8330, Bosutinib, BMS-536924, Lestaurtinib, PD 98059, OTSSP167, and 5z-7-oxozeanol target MAP2K1.

 **bgyori** 1:24 AM  
how frequently is BRAF mutated in melanoma?

 **clare** APP 1:24 AM  
Sorry, I'm not sure what that means.

 **bgyori** 1:24 AM  
AutoPattern: FindMutationFrequency "how frequently is BRAF mutated in melanoma?" BRAF:gene melanoma:disease

 **clare** APP 1:24 AM  
Alright, I added an AutoPattern.

 **bgyori** 1:24 AM  
with what frequency is EGFR mutated in glioblastoma?

 **clare** APP 1:24 AM  
I know that the mutation frequency of EGFR in glioblastoma is 23.66%.

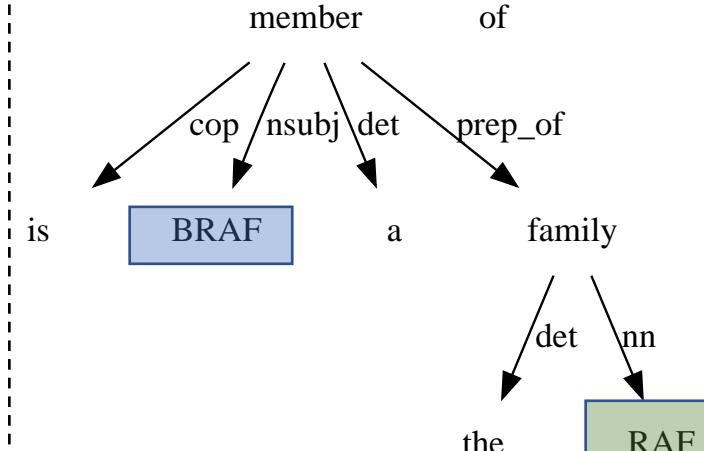
# Cascade of NLP modes in CLARE

## Regular expression templates

is **BRAF** a member of the **RAF** family

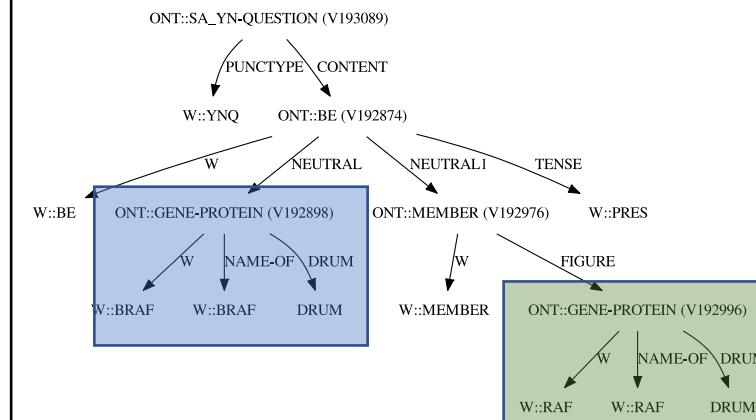
Example: Is BRAF a member of the RAF family?

## Syntactic dependency graph



(not actually used but possible)

## Semantic interpretation graph



# Not sure who is teaching who 😊

 **anna niarakis** 11:50 PM Say hello AI BLOSS

 **clare** APP 11:50 PM Sorry, I'm not sure what that means.

 **anna niarakis** 11:50 PM is IL6 involved in COVID19

 **clare** APP 11:51 PM Sorry, I'm not sure what that means.

 **anna niarakis** 11:51 PM how does IL6 interact with SARS-CoV2?

 **clare** APP 11:51 PM Overall, I know that IL6 and severe acute respiratory syndrome coronavirus 2 can interact in the following ways: activation, increase amount, and complex formation.

You can browse the full set of 4 statements here: <https://s3.amazonaws.com/indrabout-results/6cf8e872-cfbc-4688-86c4->

New

## INDRA Results

### Statements

		<a href="#">Collapse All</a>
	databases	<a href="#">phosphosite</a> <a href="#">cbl</a> <a href="#">pc11</a> <a href="#">biopax</a> <a href="#">bel_lc</a> <a href="#">signor</a> <a href="#">biogrid</a> <a href="#">lincs_drug</a> <a href="#">tas</a> <a href="#">hprd</a> <a href="#">trust</a> <a href="#">ctd</a> <a href="#">virhostnet</a> <a href="#">phosphoelm</a> <a href="#">drugbank</a> <a href="#">omnipath</a>   <a href="#">rlimp</a> <a href="#">isi</a> <a href="#">tees</a> <a href="#">geneways</a> <a href="#">eidos</a> <a href="#">trips</a> <a href="#">medscan</a>
	sparser	<a href="#">reach</a>
	reading	
		Severe acute respiratory syndrome coronavirus 2 affects IL6
		Severe acute respiratory syndrome coronavirus 2 activates IL6.
		Severe acute respiratory syndrome coronavirus 2 activates IL6. <a href="#">1 / 8</a>
	eidos	"SARS-CoV-2" mainly causes a dramatic increase in IL-6 and does not remarkably promote other pro-inflammatory factors, such as IL-1beta and IFN-gamma." <a href="#">32754163</a>
		Severe acute respiratory syndrome coronavirus 2 increases the amount of IL6.
		Severe acute respiratory syndrome coronavirus 2 binds IL6.
		IL6 binds severe acute respiratory syndrome coronavirus 2. <a href="#">1 / 1</a>
	reach	"SARS-CoV-2", severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; IL, interleukin; mIL-6R, membrane bound interleukin-6 receptor; gp 130, glycoprotein 130; MCP-1, monocytes chemoattractant protein-1; GM-CSF, granulocyte-macrophage colony stimulating factor; JAK-STAT, Janus kinase and signal transducer and activator of transcription. Figure 5 : REPROGRAM consortium pathway for targeting cytokine storm in severe or critically ill COVID-19 patients." <a href="#">32754159</a>

# Availability

- EMMAA: emmaa.indra.bio
  - Github: <https://github.com/indralab/emmaa>
  - Documentation and reports: <https://emmaa.readthedocs.io>
- INDRA: indra.bio
  - Github: <https://github.com/sorgerlab/indra>
  - Documentation: <https://indra.readthedocs.io>
- INDRA Database: db.indra.bio
- Other projects: <https://indralab.github.io>

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Disease Map Community for vibrant  
discussions and exchanges!

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THANK YOU  
FOR  
YOUR  
ATTENTION  
ANY QUESTIONS?

